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Hybrid polarizable simulations of a conventional Hydrophobic PolyElectrolyte. Towards a theoretical tool for Green Science innovation.

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Abstract

1
2 Hybrid modeling approaches based on *all-atom* force fields to handle a
3 solute and coarse grained models to account for the solvent are promising nu-
4 merical tools that can be used to understand the properties of large and multi
5 components solutions and thus to speed up the development of new industrial
6 products that obey the standard of green and sustainable chemistry. Here we
7 discuss the ability of a full polarizable hybrid approach coupled to a standard
8 Molecular Dynamics scheme to model the behavior in aqueous phase and at
9 infinite dilution conditions of a standard hydrophobic polyelectrolyte polymer
10 whose charge is neutralized by explicit counter ions. Beyond the standard pic-
11 ture of a polyelectrolyte behavior governed by an interplay between opposite
12 intra polyelectrolyte and inter polyelectrolyte/counter ion Coulombic effects,
13 our simulations show the key role played by both intra solute polarization ef-
14 fects and long range solute/solvent electrostatics to stabilize compact globular
15 conformations of that polyelectrolyte. Our full polarizable hybrid modeling ap-
16 proach is thus a new theoretical tool well suited to be used in digital strategies
17 for accelerating innovation for Green Sciences, for instance.

18 1 Introduction

19 Developing new products that obey the standards of green and sustainable chem-
20 istry with eco-sustainable ingredients is presently a major goal of many industries
21 ranging from chemistry, oil manufacturers, personal care or cosmetics. However,
22 because of the complexity of most of the solutions/emulsions that these industries
23 use, the development of new, safe and biodegradable products is a particularly chal-
24 lenging task. For instance, standard oil-in-water emulsions, for cosmetic purpose for
25 instance, comprise several components like neutral/charged flexible macromolecules,
26 anionic/zwitterionic surfactants as well as salts and alcohols, and lots of efforts fo-
27 cus today in making such formula more and more natural by substituting historical
28 compounds by naturally-derived molecules, *e.g.* polysaccharides¹. However these
29 kinds of emulsions correspond to complex multi-phasic systems whose properties
30 are highly sensitive to the substitution/addition of new compounds and most of the
31 inherent mechanisms that are involved in systems under such conditions are still
32 poorly understood.

33 To substitute a component in a solution, a strategy consists in understanding
34 how it interacts with its partners and to select a substitute able to play a similar
35 role. This can be *a priori* achieved from experimental data, in particular microscopic
36 structural ones or from physico-chemically equivalent parameters matching. How-
37 ever investigating experimentally the microscopic structures of complex molecular
38 assemblies in solution is still a challenging task in modern chemistry and materials
39 science^{2,3}. Regarding macromolecular polymeric systems for instance, Atomic Force
40 Microscope, AFM, imaging technique is able to provide mesoscopic pictures of them
41 in various environments at best at the 10 nm scale⁴⁻⁷. Small Angle Neutron and
42 X-ray Scattering, SANS/SAXS, techniques are also commonly used to investigate
43 polymer-based solutions⁸⁻¹¹ even if the interpretation of their data may be contro-
44 versial.¹² To tackle out the lack of experimental data, molecular simulations are a

45 valuable alternative. Since the nineties, computer Monte-Carlo, MC, and Molecular
46 Dynamics, MD, simulations started to play an important role to understand the
47 properties of polymer-based solutions, see Refs^{13,14} for instance. These simulations
48 are performed using different theoretical approaches, from pure *all-atom* schemes
49 for which all the system components (solute, solvent and counter ions) are mod-
50 eled at the same level of accuracy to hybrid approaches for which the solvent can be
51 accounted for implicitly. For instance in 2009 Yethiraj and co-workers reported simu-
52 lations performed using pure *all-atom* and hybrid approaches of simple Hydrophobic
53 PolyElectrolyte, HPE, systems comprising at most 384 beads^{15,16}. Today with the
54 on-going increase of the available computational resources, more realistic *all-atom*
55 simulations are commonly performed to investigate the properties of polyelectrolytes
56 in aqueous phase. Besides simulations based on standard Lennard-Jones, LJ, po-
57 tentials (see the recent studies Refs.¹⁷⁻²⁰), MD simulations at the 100 *ns* scale of
58 large hydrated polyelectrolyte systems (comprising up to 250k atoms) performed
59 using standard pairwise force fields (and lattice-based Ewald summation techniques
60 to account for long range electrostatics) are now regularly reported, see Refs.²¹⁻²³
61 for instance.

62 Despite the impressive progress of molecular modeling techniques, simulations
63 of complex multi-components solutions/emulsions are still not routinely performed.
64 That arises from the atomic size of realistic emulsions that are at the very least one
65 to two order of magnitude larger than the systems simulated in the above studies.
66 Moreover most of the simulations performed today rely on standard additive force
67 fields that are acknowledged for their inability in accurately modeling charged sys-
68 tems in a polar medium like water, from single ion²⁴⁻²⁷ to ionic liquids^{28,29} and all
69 hydrated polyelectrolyte systems³⁰. That results from the inability of additive force
70 fields to model the inherent non-pairwise character of microscopic polarization, a
71 pivotal force to understand the interaction involving charged species, see Fig. 1.

72 Here we present a simulation work based on a new polarizable hybrid molecu-

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lar simulation approach a priori well suited for accelerating innovation with digital
strategies for Green Sciences. That approach relies on modeling interactions among
non-solvent atoms using the *all atoms* polarizable force field TCPEp, which is based
on a polarizable induced dipole moment approach³¹, like the one of Fig. 1. How-
ever polarizable force fields are computationally demanding, not only because of the
polarization computational cost (in particular as using Drude oscillators³²) but also
because usually such force fields also consider more sophisticated interaction poten-
tials to model electrostatic effects (like the force field AMOEBA that accounts for
atomic static dipoles and quadrupoles³³) or short range electronic density reorgani-
zation phenomena, like TCPEp³¹.

To perform efficiently MD simulations in aqueous phase by means of polarizable
force fields, one of us proposed to handle water using the multi-level Polarizable
Pseudo Particle, \mathbf{PPP}^l , coarse-grained, CG, approach³⁴⁻³⁶. \mathbf{PPP}^l belongs to the
macroscopic Density Functional Theory field. However as it retains the notion of
particles, it also allows for an explicit solvent representation that is recommended
for a realistic modeling of polyelectrolytes¹⁸. Moreover as \mathbf{PPP}^l relies on a polariz-
able induced dipole moment approach, it can be readily coupled to *all-atom* induced
dipole moment-based polarizable force fields like AMOEBA and TCPEp³⁷. Two
important features of the \mathbf{PPP}^l approach are (1) to readily allow simulations in
infinite dilution conditions and (2) to permit the modulation of the spatial range of
the solvent electrostatic effects on a solute. That second feature allows the modu-
lation the apparent solvent dielectric constant by taking constant the intensity of
local interactions between the solvent particles and the solute³⁶. As compared to
standard *all-atom* simulations based on periodic condition schemes, the \mathbf{PPP}^l ap-
proach thus allows one to investigate the properties of a HPE in water-like solutions
that are fully disentangled from solute concentration effects, as well as to discuss the
role of solvent macroscopic properties (in particular the magnitude of its dielectric
constant).

101 The current work aims at showing the ability of the hybrid \mathbf{PPP}^l /TCPEp ap-
102 proach to model the complex components of industrial solutions and thus at paving
103 the way in developing new digital workflows allowing to speed up the development
104 of Natural products based on the knowledge of conventional ones. To this aim, we
105 first focus on investigating the behavior of a generic mid-size HPE copolymer that is
106 commonly used in conventional chemical industry for water/wastewater treatments,
107 personal care as well as for clean and renewable energy production^{38–42}.

108 The HPE we consider, that is schematically depicted in Fig. 2, possesses a fraction
109 f_c of charged groups per copolymer unit equals to 0.7, and independent from usual
110 pH conditions. We denote that Polyelectrolyte as **P70** (because of its total charge :
111 $+70 e$) and we simulate it in two water-like solutions at infinite dilution conditions by
112 means of MD simulations and of our hybrid approach : **P70** and its Cl^- counter ions
113 are modeled by the *all-atom* polarizable TCPEp force field whereas the water-like
114 environments are handled by the \mathbf{PPP}^l CG approach. In particular we simulated
115 the **P70** collapse from a linear conformation as dissolved in pure (*i.e.* salt free)
116 \mathbf{PPP}^l box that comprised about 0.9M solvent particles. The dielectric constant of
117 that environment is one order of magnitude smaller than for liquid water. Then we
118 investigated the effect of the solvent dielectric constant on the stability of the **P70**
119 collapsed structures by simulating them embedded in a eight times more extended
120 \mathbf{PPP}^l medium whose dielectric constant is close to the liquid water one.

121 Less attention has been paid to investigate the role of polarization on HPEs than
122 on bio-molecular polyelectrolytes like DNA/RNA^{43–45} and charged polypeptides⁴⁶.
123 HPE properties in aqueous phase are usually inferred to arise from a interplay of
124 microscopic interactions, namely intra HPE Coulombic repulsion and effective at-
125 traction resulting from hydrophobic effects^{47,48}. We thus simulated a non-polarizable
126 **P70** in our two \mathbf{PPP}^l media in order to further discuss the role of polarization on
127 hydrated HPEs beyond the standard Coulombic picture^{49–53}.

128 As far as we know no experimental data regarding the conformational behav-

ior of **P70**-like HPEs in water are available contrary to sulfonated polystyrenes for
instance, see in particular Refs.^{11,54}. To assess the reliability of our computational
protocol we will also briefly present simulation results regarding hydrated carboxy-
lated polystyrenes whose degree of carboxylation (charge fraction) varies from 0 to
1 an whose properties may be reasonably expected to be close to those of sulfonated
polystyrenes.

2 Theoretical methods

2.1 The all-atom force field

The *all-atom* polarizable force field TCPEp³¹ is based on a total potential energy U of a molecular system decomposed into a sum of six contributions

$$U = U^{rep} + U^{qq'} + U^{pol} + U^{lh} + U^{disp} + U^{intra}. \quad (1)$$

The last energy term is the sum of the standard stretching, bending, improper torsional and dihedral torsional energy terms modeling the interactions among covalently bonded atoms. The first two terms correspond to the inter atomic short range repulsion and to Coulombic interactions

$$U^{rep} = \sum_{i=1}^N \sum_{j>i}^{N^*} A_{ij} \exp(-B_{ij}r_{ij}),$$
$$U^{qq'} = \sum_{i=1}^N \sum_{j>i}^{N^*} \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}}.$$

r_{ij} is the distance between atoms i and j , the q_i s are the static charges located on atomic centers, and A_{ij} and B_{ij} are adjustable parameters. N is the total number of atoms within the molecular system and the superscript * indicates that the corresponding sum includes only pairs of atoms separated by more than two chemical

141 bonds. The repulsive term is truncated for distances r_{ij} greater than 5 Å.

The polarization energy term U^{pol} is based on an induced dipole moment approach. Induced dipole moments $\{\mathbf{p}_i\}_{1 \leq i \leq N_\mu}$ are introduced, one per polarizable non-hydrogen atom. They obey

$$\mathbf{p}_i = \alpha_i \cdot \left(\mathbf{E}_i^q + \sum_{j=1}^{N_\mu^*} \mathbf{T}_{ij} \cdot \mathbf{p}_j \right). \quad (2)$$

The static charge electric field \mathbf{E}_i^q acting on a polarizable atom i is generated only by the charges of the $N_{\mathbf{E}}$ surrounding atoms belonging to charged or dipolar chemical moieties. The N_μ and $N_{\mathbf{E}}$ sets do not necessarily match to each other. Let us consider the molecule HO-CH₂-CH₂-CH₂-CH₂-NH₃⁺: only its first three atoms HO-C (alcoholic moiety) and its last four ones C-NH₃⁺ (cationic head) belong to the $N_{\mathbf{E}}$ set, and only its carbon and oxygen atoms are polarizable centers. α_i is the isotropic polarizability of the polarizable atom i and \mathbf{T}_{ij} is the dipolar interaction tensor. The static electric fields and dipolar tensors include short range Thole-like damping functions⁵⁵ that vanish for interatomic distances greater than 5 Å. The set of Eqs. 2 is iteratively solved and the resulting polarization energy term U^{pol} is

$$U^{pol} = \frac{1}{2} \sum_{i=1}^{N_\mu} \frac{\mathbf{p}_i^2}{\alpha_i} - \sum_{i=1}^{N_\mu} \mathbf{p}_i \cdot \mathbf{E}_i^q - \frac{1}{2} \sum_{i=1}^{N_\mu} \sum_{j=1}^{N_\mu^*} \mathbf{p}_i \mathbf{T}_{ij} \mathbf{p}_j. \quad (3)$$

142 The term U^{disp} models microscopic dispersion effects that are pivotal to describe
143 hydrophobic alkyl chains. It is a sum of basic C_{ij}/r_{ij}^6 terms where the $C_{ij} (<0)$ are
144 ajustable parameters. For our purpose only non-hydrogen atoms are considered as
145 dispersion centers. To model particular electronic density reorganization effects (as
146 those occurring within acrylamide hydrogen bonds), TCPEp also includes a set of
147 short-range cooperative energy terms denoted U^{lh} that are very close to the terms
148 we introduce to model accurately water hydrogen bond networks⁵⁶. For the present
149 study such energy terms are taken into account to model the interactions among

150 the **P70** acrylamide moieties. However they play a negligible role in our simulations
151 and they will not be further discussed.

152 2.2 Force field parameters

153 TCPEp parameters are adjusted to reproduce high-level *ab-initio* quantum data
154 regarding a training set of small molecular systems (like the atomic charges that are
155 assigned to reproduce the dipole moment of neutral molecules and the charges of
156 charged molecules to meet those computed from the quantum Natural Population
157 Analysis scheme⁵⁷). **P70** can be decomposed in a set of chemical groups for which
158 we have already assigned accurate parameters^{35,36,58–60}, at the exception of a reduced
159 set of parameters regarding the torsional degrees of freedom of the dimethyldiallyl
160 ammonium five membered ring that were specifically assigned for the present study
161 according to the protocol detailed in Ref.⁵⁹.

162 Regarding alkyl groups, their parameters (mainly repulsion and dispersion) were
163 assigned to reproduce the quantum binding energy ($-0.5 \text{ kcal mol}^{-1}$) and geometry (a
164 carbon/carbon equilibrium distance of 3.5 \AA) of the methane dimer in gas phase as
165 predicted by quantum CCSD(T) computations at the Complete Basis Set limit⁶¹.
166 Because of the very weak permanent dipole in alkanes, we assume in the present
167 study that only short range repulsion and dispersion govern the interactions involv-
168 ing alkyl groups in absence of external electric fields. We thus systematically neglect
169 Coulombic interactions and static charge electric fields arising from alkyl moieties.
170 However we consider the alkyl carbons as polarizable centers (their isotropic polar-
171 izability is set to 2.1 \AA^3) and they undergo the static charge and/or induced dipole
172 electric fields generated by all the chemical moieties surrounding them.

173 Lastly, we use no long range truncation scheme as computing Coulombic in-
174 teractions and static charge electric fields regarding **P70** and its counter ion cloud,
175 whereas we truncate all their induced dipole/induced dipole interactions correspond-
176 ing to distances larger than 12 \AA .

177 **2.3 The multi-level coarse-grained water model PPP^l**

178 The main feature of the water coarse-grained approach **PPP^l**³⁵⁻³⁷ is to model a
179 single three atomic water molecule or a set of water molecules by a single polarizable
180 pseudo-particle (denoted as PPP) whose polarizability α_s obeys a Clausius-Mosotti
181 relation:

$$\alpha_s = \frac{\epsilon_s - 1}{4\pi\rho_s\epsilon_s}, \quad (4)$$

182 here, ϵ_s and ρ_s are the dielectric constant and the particle density of liquid water
183 (a quantity that is proportional to the inverse of the water molecular volume). α_s
184 is thus a linear function of the PPP volume. Another important assumption is the
185 use of the *local* approximation : the intensity of the induced dipole moment \mathbf{p}_j^s
186 corresponding to PPP j is modulated only by the solute electric field $\mathbf{E}_{\text{solute}}^j$ acting
187 on j , *i.e.* the PPPs don't polarize each other. However that can yield to largely
188 overestimate solute/PPP polarization effects up to unphysical values in particular
189 situations. To prevent such artefacts, **PPP^l** allows the \mathbf{p}_j^s s to saturate according
190 to³⁴

$$\mathbf{p}_j^s = \mu_s \mathcal{L} \left(\frac{3\alpha_s \mathbf{E}_{\text{solute}}^j}{\mu_s} \right) \frac{\mathbf{E}_{\text{solute}}^j}{|\mathbf{E}_{\text{solute}}^j|}, \quad (5)$$

191 here \mathcal{L} is the Langevin function and μ_s is the PPP saturation dipole value. The
192 corresponding PPP/solute polarization energy is then

$$U_{ps}^{pol} = -\frac{\mu_s^2}{3\alpha_s} \sum_{j=1}^{N_s} \ln \left[\frac{\sinh(3\alpha_s |\mathbf{E}_{\text{solute}}^j| / \mu_s)}{3\alpha_s |\mathbf{E}_{\text{solute}}^j| \mu_s} \right]. \quad (6)$$

193 Here N_s is the number of PPPs. Note that for both the above equations and
194 weak solute electric fields, the linear regime corresponding to Eqs. 2-3 is recovered.

195 The polarizability α_s of the PPPs accounts not only for the solvent electronic po-
196 larization induced by the solute but also for the solvent orientational polarization³⁴.

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197 As such α_s does not correspond to a standard atomic or a molecular polarizability
198 (which models only the perturbation of an electronic cloud by an external electric
199 field). Moreover the α_s allows one to consider PPPs of different sizes. As modeling
200 a HPE by means of an *all-atom* force field, the natural choice is to set the size of all
201 the PPPs to that of a single water molecule (that yields a PPP polarizability of 2.35
202 \AA^3). Moreover, within the **PPP**^{*l*} framework, we assume solute/solvent long range
203 electrostatic contributions arising from neutral solute groups to be negligible. We
204 thus systematically truncate both the induced dipole and static charge components
205 of the corresponding electric fields $\mathbf{E}_{\text{solute}}^j$ for solute atom/PPP distances greater
206 than the cut off distance $R_{\text{cut}}^{\text{pol},1}$.

207 However the above spherical truncation scheme not only yields large underesti-
208 mation of ion hydration energies but also large artefacts in modeling ion association
209 (see Ref.³⁶ and references cited therein). To remediate both these drawbacks we pro-
210 posed the multi-level scheme **PPP**^{*l*} to model efficiently the long-range electrostatic
211 interactions between a charged solute and farther (and farther) solvent domains³⁶.
212 Within a shell lying at the vicinity of the charged solute (that shell extends to no
213 more than $R_{\text{cut}}^{\text{pol},1}$ from any non hydrogen solute atom) that multi-level approach
214 considers PPPs whose size matches that of a water molecule. These first solvent
215 level PPPs ($l = 1$) undergo the static charge electric field generated by all the solute
216 charged groups (and the truncated static and dipole electric field components arising
217 from neutral groups). To model solute/solvent interactions at longer distances than
218 $R_{\text{cut}}^{\text{pol},1}$, larger (and larger) PPPs are introduced according to the scheme shown in
219 Fig. 3. These larger PPPs define higher level ($l > 1$) solvent shells. They undergo
220 the static charge electric field generated by all the solute charged groups if they lie
221 within a shell surrounding the solute and extending from $R_{\text{cut}}^{\text{pol},l-1}$ to $R_{\text{cut}}^{\text{pol},l}$ from it.
222 The solute/solvent polarization term $U_{ps,l>1}^{\text{pol}}$ corresponding to each $l > 1$ PPP level
223 is taken under the linear form

$$U_{ps,l>1}^{\text{pol}} = \frac{1}{2} \sum_{i=1}^{N_{\mu}^{l>1}} \frac{\mathbf{P}_i^2}{\alpha_s^{l>1}} - \sum_{i=1}^{N_{\mu}^{l>1}} \mathbf{P}_i \cdot \mathbf{E}_i^q. \quad (7)$$

224 Here, $N_{\mu}^{l>1}$ are the number of $l > 1$ PPPs, $\alpha_s^{l>1}$ is their polarizability, according
225 to Eq. 4, and \mathbf{E}_i^q is the static charge electric field generated by the solute charged
226 groups on these PPPs.

227 Besides largely improving the modeling of ion hydration and ion association, we
228 also showed that multi-level approach to allow an efficient modeling of particularly
229 large and extended solvent domains at the μm scale and above³⁶. For the present
230 study, we consider two **PPP**^{*l*} solvent approaches. The first, denoted Short Range
231 PPP, **SRP**, models the solvent by means of only first level PPPs and by setting
232 the shell-based cut off distance $R_{\text{cut}}^{\text{pol},1}$ to 12 Å. The second approach, denoted Long
233 Range PPP, **LRP**, considers also a second level of PPPs made of particles that are
234 8 times larger than the first level ones. Their polarizability is thus $\alpha_{s,2} = 18.8 \text{ \AA}^3$.
235 The second level PPPs undergo the static charge electric field generated the **P70**
236 charged groups if these PPPs are located within a shell encompassing the HPE from
237 $R_{\text{cut}}^{\text{pol},1} = 12$ to $R_{\text{cut}}^{\text{pol},2} = 143$ Å. In an earlier study³⁶ we showed the **SRP** approach to
238 reinforce the association of oppositely charged ions and the repulsion of charge-like
239 ions as compared to liquid water (the apparent dielectric constant of a first level
240 PPP solution is one order of magnitude weaker than that of liquid water), whereas
241 the **LRP** approach already provides a description of ion pairing agreeing with that
242 expected in liquid water. The dielectric constant of the **LRP** medium is thus close
243 to the liquid water one.

244 Within the multi level **PPP**^{*l*} approach, only electrostatic solute/ $l > 1$ PPPs in-
245 teractions are taken into account. Regarding first level PPPs, their non-electrostatic
246 interactions with solute atoms are modeled by means of a Lennard-Jones-like poten-
247 tial corresponding to a stronger repulsion³⁷ to which is added a specific short range
248 many-body term to prevent over populated first hydration shell at the vicinity of

249 charged species³⁶. The corresponding force field parameters for first level PPPs are
250 assigned to reproduce both the first hydration shell structure and the hydration
251 Gibbs energy of a training set of small solutes and ions³⁶. For the present purpose
252 we used an updated parameters that will be discussed elsewhere.

253 Interactions among first level PPPs are modeled using a standard additive Lennard-
254 Jones, LJ, energy term and a many-body term that is a function of the solvent local
255 density at the vicinity of a PPP³⁵. Both these terms are truncated for inter particle
256 distances greater than $R_{\text{cut}}^{\text{PP}} = 7 \text{ \AA}$ and their parameters were assigned to reproduce
257 the liquid water density (0.0331 molecule per \AA^3) and the two regimes of the energy
258 corresponding to the creation of an empty cavity in water at ambient conditions
259 according to the Lum-Chandler-Weeks theory of hydrophobicity⁶².

260 Interactions among second order PPPs are modeled using only a LJ term that
261 is truncated for distances greater than 10 \AA . The corresponding LJ radius is twice
262 as large as for first order PPPs and the LJ intensity (denoted ϵ_2) is one order of
263 magnitude weaker than for the first level PPPs as in our original study³⁶. In that
264 original study we showed second level PPPs to be slightly over concentrated at their
265 lower cut off distance as interacting with a single monovalent ion like Na^+ and Cl^- .
266 Because of the large total charge of the **P70** (+70 e) and because of the overall large
267 number of counter ions Cl^- , our choice regarding the LJ parameter ϵ_2 can lead to
268 drawbacks like over organized **P70**/counter ions/second order PPPs structures. We
269 will discuss that particular issue in the forthcoming Section 4.

270 Contrary to the recent approach proposed by Chremos and Douglas^{17,20,63}, the
271 use of only first level PPPs or in conjunction with second level ones allows the mod-
272 ulation of the apparent dielectric constant of the solvent without altering the short
273 range solute/solvent interactions. Moreover our shell-based cutoff scheme also allows
274 the modeling of solvation at infinite dilution conditions. In our **PPP^l** approach, a
275 solute is embedded in a cubic box fulfilled with first level PPPs and that system is
276 then embedded in a larger box made of second level PPPs and so on³⁶. To maintain

277 the PPP density within each box, the PPPs are allowed to interact with their own
278 periodic images. As the long range interactions among PPPs are truncated, only the
279 first 26 periodic box images are usually needed for that task. Regarding the solute,
280 to model its solvation at infinite dilution conditions, one just needs to neglect the
281 interactions between the solute and its own periodic images. That choice is made
282 for both the solvent approaches **SRP** and **LRP**. However note that solute atoms
283 can interact with PPP images if they lie close to the box boundaries.

284 Regarding **SRP**, ignoring the interactions between the solute and its own peri-
285 odic images corresponds technically to model it as infinitively diluted. However we
286 may also interpret that solute as embedded in a confined water cavity delimited by
287 the shell of first order PPPs. That interpretation is supported by the modeling of
288 the short range solute/PPP interactions using the same potential energy terms in
289 both the **SRP** and **LRP** approaches.

290 We assume here first level PPPs (those who interact at short range with the so-
291 lute) to be symmetric. Other choices are possible as considering a triatomic molecule
292 holding a permanent dipole like the isolated water molecule. However we may note
293 that the isotropic polarizability of Equation 4 allows to account for both the solvent
294 orientational and electronic polarization induced by a solute³⁴. Moreover modeling
295 the solvent using triatomic molecules will lead the approach to be less computa-
296 tionally efficient, at least by factor 3.

297 **2.4 Molecular Dynamics details**

298 MD simulations are performed at ambient conditions using the code POLARIS(MD)⁶⁴.
299 The Newtonian equations of motion are solved using a multiple-time-steps algorithm
300 with two time steps: 0.25 *fs* for intra-solute stretching, bending and improper tor-
301 sional energy terms and 2 *fs* for all the other interactions. All the covalent X–H
302 bonds and H–X–H angles are constrained to their force field reference values by
303 means of the iterative RATTLE procedure (the convergence criterion is set to 10^{-5}

304 Å). The system temperature (and pressure) in NVT and NPT simulations are mon-
305 itored by means of the Langevin dynamics approach detailed in Ref.⁶⁵ and of the
306 Nosé-Hoover barostat⁶⁶, respectively. Solute atom and PPP induced dipole mo-
307 ments are iteratively solved until the mean difference in these dipoles between two
308 successive iterations is less than 10^{-6} Debye.

The center of mass of the **P70**/counter ions system is regularly reset to the simulation box center (and the PPP coordinates updated accordingly) along our MD simulations. However to prevent any solute atom to leave that box we also consider the repulsive potential $U_{\text{box}}^{\text{rep}}$ acting only at the simulation box boundaries in order to restrain the solute atoms within the simulation box core. Let us consider a solute atom whose cartesian coordinates are (x, y, z) and a simulation box whose dimensions are (L_x, L_y, L_z) , $U_{\text{box}}^{\text{rep}}$ is defined as

$$U_{\text{box}}^{\text{rep}} = \sum_{\xi=x,y,z} k [\max(2|\xi| - (L_\xi - \delta L), 0)]^2, \quad (8)$$

309 here k and δL are two constant parameters that are set for the present study to 5 kcal
310 mol⁻¹ Å⁻² and 3 Å, respectively. $U_{\text{box}}^{\text{rep}}$ and all its derivatives vanish for solute atoms
311 located within the simulation box and farther than δL from its boundaries. Because
312 of the dimensions of our cubic boxes (at least 90 Å) the effect of that potential is
313 very weak (to not say negligible) on the **P70** and counter ions dynamic.

314 3 Results and discussion

315 3.1 The collapse of **P70** in the SRP medium

316 3.1.1 Simulation starting structure

317 The simulation Linear Starting Structure, LSS, of **P70** is shown in Fig. 2. The
318 **P70** total electrostatic charge is neutralized by adding 70 Cl⁻ counter ions that are
319 successively set on the nodes of a cubic grid in which the LSS is set (the grid node

320 dimension is 3 Å). A counter ion is set on a node (1) to minimize the Coulombic
321 interaction energy between it and **P70** and all the already added counter ions, and
322 (2) so that the shortest distance between it and any **P70** non hydrogen atom is
323 larger than 3.5 Å. The resulting **P70**/counter ions structure is then set in a cubic
324 box fulfilled with PPPs that are set on all the nodes of the above grid that are distant
325 by more than 3 Å from any non-hydrogen/counter ion atom. To solvate **P70** in its
326 LSS conformation, a large cubic box whose volume is 301^3 \AA^3 and comprising about
327 0.9M PPPs is needed to ensure that there is at least a distance of 12 Å between any
328 solute atom and the box boundaries, see Fig. 2.

329 3.1.2 **P70** structural evolution

330 We performed 8 independent MD simulations at the 2 ns scale of the **P70**/counter
331 ions system in the NPT ensemble as dissolved in the **SRP** medium. Each simulation
332 corresponds to a different set of starting atom/particle velocities randomly set and
333 corresponding to a temperature of 300 K. Along the first 200 ps simulation segments,
334 we constrained **P70** to its LSS using a harmonic potential restraining the position
335 of its nitrogens. That potential was then removed. We plot in Fig. 4 the temporal
336 evolution of the polymer gyration radius R_g and of the ratio R^{inertia} between the
337 largest and smallest **P70** inertia moment values.

338 As soon as the harmonic potential preventing polymer structural transitions is
339 removed, R^{inertia} evolves to reach a value included within 1 and 2 and R_g converges
340 towards a value of $14 \pm 0.2 \text{ \AA}$ within at most 1.2 ns, regardless of the simulation.
341 **P70** collapses thus rapidly towards a Compact Quasi Spherical, CQS, conformation,
342 see Fig. 2. Note that we performed also these simulations however in the NVT
343 ensemble (see our protocol detailed in Section 2.4) from a starting structure relaxed
344 by performing a NPT MD run along which the linear **P70** structure is harmonically
345 constrained. Along these NVT trajectories, **P70** collapses again towards a CQS
346 conformation but usually at a slower rate (at least not before 2 ns). To our opinion

347 that difference in the collapsing time scales arises from the thermostat and barostat
348 that we consider. That may also explain the much longer time needed by **P70** to
349 collapse along our **LRP** simulations that are performed in the NVT ensemble (see
350 below).

351 The **P70** compact conformations at the end of each simulation differ at the
352 atomic level. For instance the Root Mean Square Deviation, RMSD, of the ammo-
353 nium nitrogens N_a , among the 8 final simulation snapshots amounts to 7 Å. However
354 the structural properties of the ammonium groups within these final conformations
355 are close on average. In Fig. 4 we plot the radial N_a/N_a pair distribution functions
356 g_{NN} as computed along the last 500 *ps* simulation segments as well as the mean
357 numbers $N_{N_a}(r)$ of N_a atoms lying within a sphere of radius r from the Polymer
358 Center of Mass PCOM (*i.e.* the integrals of N_a /PCOM radial distribution func-
359 tions). These plots show all the N_a conformations to be very close at the end of each
360 independent simulation. Hence **P70** evolves towards different compact conforma-
361 tions whose cationic charge distribution (that governs the electrostatic interactions
362 within the polymer and between the polymer and its chemical environment) are
363 close, suggesting these conformations to be iso-energetic in the **SRP** medium.

364 Regarding counter ions, we plot in Fig. 4 their mean radial distribution functions
365 g_{ci} from PCOM, computed from the last 500 *ps* simulation segments, as well as their
366 integrals yielding the mean number of counter ions N_{ci} within a sphere of radius r
367 from PCOM. The functions g_{ci} are close : they present two peaks located at 15 and
368 23 ± 1 Å from PCOM and encompassing 5 and 68 ± 1 counter ions, respectively.
369 About 8% of the counter ions are thus absorbed on the **P70** surface whereas 90% of
370 them are located in a more distant shell extending from 4 to 21 Å from the polymer
371 surface. Lastly, at most 2 counter ions are present within the polymer CQS core
372 and only one is released far away from **P70** along a single simulation. Counter
373 ions were distributed all along the **P70** LSS. The counter ions undergo relatively
374 large displacements at the early stages of our simulations before to form a spherical

375 cloud. In the starting linear structure the counter ions mainly interact only with
376 a few cationic charges of **P70** whereas they interact all with all the **P70** cationic
377 charges located in rather small spherical volume at the end of the simulations.

378 In Fig. 4 we also plot the radial distribution functions $g_{\text{PPP}}(r)$ between the PPPs
379 and PCOM as well as their integrals $N_{\text{PPP}}(r)$. The functions $g_s(r)$ are converged
380 to their expected bulk value for PPP/PCOM distances $r \leq 30 \text{ \AA}$, *i.e.* at about
381 16 \AA from the **P70** surface. We note also (1) a depletion of the PPP density at
382 the vicinity of the polymer surface, that may be interpreted as resulting from the
383 hydrophobic nature of **P70**, and (2) by a PPP density reinforcement in between the
384 **P70** surface and the external counter ions shell. Lastly a far from negligible number
385 of PPPs (about 270) are trapped within the core of the **P70** CQS conformations :
386 their density within the **P70** spherical volume is $0.024 \text{ PPPs per \AA}^3$, a value 40 %
387 weaker than within the solvent bulk.

388 To assess the stability of a **P70** CQS conformation on longer simulation times, we
389 select a final CQS structure (together with its counter ion cloud) from one the above
390 independent simulations. That structure is embedded in a new cubic box whose
391 volume is 90^3 \AA^3 and comprising 23k PPPs. We then performed a 500 *ns* scale NPT
392 MD simulation of that solvated system. Along the new simulation, **P70** jumps from
393 its starting structure towards more and more different ones (the $\text{RMSD}(N_a)$ value
394 increases up to 5 \AA) but the new structures all correspond to CQS conformations,
395 see the superimposition of **P70** structures in Fig. 5. Along that 500 *ns* simulation,
396 the counter ion cloud and solvent structural properties all agree with those discussed
397 above. Hence, in a salt free **SRP** medium and at infinite dilution conditions, the
398 **P70** structure fluctuates between different CQS conformations whose properties are
399 close on time intervals close to the μs scale. However we can not conclude from our
400 simulations on the thermodynamical nature (global minima of the potential energy
401 surface or transient structures⁶⁷) of these CQS conformations.

402 3.1.3 Energies

403 To discuss the energetic data, we performed a single 1 *ns* NPT simulation of **P70**
404 constrained in its LSS conformation and embedded together with its counter ion
405 cloud within a 0.9M first order PPP cubic box. The mean values of all the interaction
406 energy components computed from the last 800 *ps* segment of that simulation are
407 taken as the reference energy values at the beginning of the HPE collapse process.

408 In Fig. 6, we plot the temporal evolutions of the total intra-**P70** and intra-counter
409 ions energies, of the **P70**/PPPs and counter ions/PPPs polarization energies, and of
410 the total **P70**/counter ions interaction energy as soon as the polymer constraints are
411 removed along our independent simulations. The dispersion in these energy values
412 among the simulations is weak (at most 1 %) showing all the final **P70**/counter
413 ions structures to be close in energy, as expected from the similarity of the **P70**
414 charge distribution at the end of all the simulations. Because of the large **P70**
415 electrostatic positive charge (+70 *e*) and thus from the large negative charge of the
416 counter ion cloud, there is a large increase in both the intra polymer ($\Delta\bar{U}_p$) and
417 intra counter ions ($\Delta\bar{U}_{ci}$) energies during the polymer collapse process : $\Delta\bar{U}_p$ and
418 $\Delta\bar{U}_{ci}$ amount to about +25 and +15 10^3 kcal mol⁻¹, respectively. However these
419 large energy increases are largely counter balanced by strong stabilizing **P70** and
420 counter ions polarization interactions with the solvent, as well as by strong stabilizing
421 **P70**/counter ions interactions : during the polymer collapse process, the decreases
422 $\Delta\bar{U}_{ps}$, $\Delta\bar{U}_{cs}$ and $\Delta\bar{U}_{pc}$ in the energies corresponding to the latter interactions amount
423 to -5, -16 and -35 10^3 kcal mol⁻¹, respectively.

424 Within our hybrid modeling framework, the collapse of **P70** towards CQS con-
425 formations in a **SRP** medium is driven by a competition between (1) strong desta-
426 bilizing intra-**P70** and intra-counter ion cloud interactions and (2) strong stabilizing
427 **P70**/solvent and **P70**/counter ions ones. By analyzing in details the main compo-
428 nents of the interaction energies (namely the repulsion, Coulombic, polarization and
429 dispersion components), interactions among counter ions are largely dominated by

430 repulsive Coulombic effects. Intra-**P70** interactions are also dominated by repul-
431 sive Coulombic effects and by far from negligible attractive polarization interactions
432 that favor **P70** CQS conformations : the variation of the intra-**P70** polarization
433 energy during the collapse process amounts to about 20% of the Coulombic one in
434 absolute values. We may also note that intra-**P70** dispersion and atomic repulsion
435 equally favor/disfavor the CQS conformations, however the corresponding energy
436 variations during the collapse process are one order of magnitude smaller than for
437 polarization. Lastly we identified no more than 7 intra-**P70** hydrogen bonds among
438 the acrylamide groups along the simulations. That corresponds to an interaction
439 energy of about 35 kcal mol⁻¹, which is negligible compared to the main intra-**P70**
440 Coulombic and polarization energy components.

441 The attractive polarization forces within the **P70** CQS conformations are tied
442 to strong alkyl carbon induced dipole moment values μ_C that can reach values as
443 large as 5 Debye. In Fig. 7, we plot the mean values of μ_C for each carbon computed
444 along all the final 500 *ps* simulation segments as a function of the mean distance of
445 the alkyl carbons from PCOM. In line with the expected intensity of electric fields
446 generated by quasi spherical positive charge distributions, the values μ_C increase as
447 the alkyl carbons are closer to the surface of **P70** in a CQS conformation. Regarding
448 the strong μ_C values, we may note here that strong induced dipole moments (larger
449 than 2 Debye) are also predicted for water lying at the vicinity of the heavy cation
450 Th(IV) or the halide anion F⁻ in liquid water by both polarizable *all-atom* force
451 field and quantum Car-Parinello simulations⁶⁸⁻⁷⁰.

452 Contrary to the present results, a large charge fraction f_c of 0.7, as for **P70**, is
453 experimentally shown to prevent a HPE to collapse towards a compact globular con-
454 formation and to favor instead elongated structures from pear-necklace to wormlike
455 ones in different environments like water and water/acetone mixtures^{6,9-11}. First a
456 non negligible fraction of the counter ions (about 8 %) are adsorbed on the **P70**
457 surface. That discharging effect yields thus a slightly weaker apparent HPE \tilde{f}_c value

458 (about 0.65) than f_c . Moreover the intra-molecular stabilizing polarization effects
459 within a **P70** CQS conformation counter balance about 20 % of the destabilizing
460 intra-polymer Coulombic interactions. We may also interpret these polarization ef-
461 fects to be responsible for a further decrease of \tilde{f}_c to about 0.5. Lastly note also (1)
462 the ionic charge to be more diluted in quaternary ammonium groups than in the
463 $-\text{NH}_3^+$ and $-\text{SO}_3^-$ ionic heads that were used to investigate the structural proper-
464 ties of HPEs as a function of f_c in Refs.^{6,9-11}; and (2) the inter ionic head distances
465 between adjacent polymer units in the highly charged poly(vinyl amine) HPEs of
466 Ref.⁶ are about twice shorter than in **P70** (see the g_{NN} data in Fig. 4 for instance).
467 That yields a still weaker \tilde{f}_c value and that explains why a HPE with a large f_c
468 value like **P70** can collapse towards a CQS conformation in a **SRP** medium.

469 3.1.4 Comparison to carboxylated polystyrenes PSC^{f_c}

470 To further discuss the reliability of our multi level simulation scheme, we investi-
471 gated the behavior of HPEs corresponding to carboxylated polystyrenes PSC^{f_c} as
472 dissolved in first order PPP boxes. Here f_c is the degree of carboxylation/charge
473 fraction that we set for the present purpose to 0.00, 0.25, 0.50 and 1.00, respectively.
474 The length of the PSC^{f_c} is 80 and their negative charge is neutralized by adding
475 Na^+ counter ions. For our purpose we consider all the carboxylates as deprotonated
476 anionic heads that are regularly spaced along the PSC^{f_c} chains. Our PSC^{f_c} are
477 similar to the sulfonated polystyrenes experimentally investigated by Boué and co-
478 workers¹¹ even if their length is about one order of magnitude shorter. Note the dis-
479 tance between two adjacent ionic heads in the linear and fully carboxylated PSC^1
480 is about 2.5 Å whereas it is at least twice as large in any **P70** CQS conformation.

481 To fully solvate the linear starting structures of the PSC^{f_c} we need smaller
482 PPP boxes as compared to **P70** : their dimensions are now about 200 Å and they
483 comprise about 260k first order PPPs. For each solvated PSC^{f_c} we performed a
484 single MD simulation at the 100 ns scale according to our MD protocol detailed

485 above. As for **P70** all the force field parameters to model intra \mathbf{PSC}^{f_c} and \mathbf{PSC}^{f_c}
486 /counter ion interactions are assigned only from quantum *ab initio* computations
487 and taken from Ref.³¹.

488 The temporal evolutions of the gyration radii R_g and the final snapshots of our
489 \mathbf{PSC}^{f_c} are provided as Supplementary Material. Contrary to **P70** the fully car-
490 boxylated \mathbf{PSC}^1 does not collapse towards a compact conformation along the 100 ns
491 trajectory: rather it slowly evolves towards a helicoidal structure stabilized by salt
492 bridges between carboxylate heads and Na^+ ions. The three other \mathbf{PSC}^{f_c} collapse
493 towards more and more compact (and less organized) conformations. In particular
494 \mathbf{PSC}^0 collapse fastly (within a few ns) towards a stable compact conformation close
495 to the **P70** CQS ones. Moreover the \mathbf{PSC}^{f_c} gyration radii decrease as f_c decreases,
496 from 22 ($f_c = 1$) down to 11 ($f_c = 0$) Å. Even if Boué and co workers¹¹ experimen-
497 tally investigated longer sulfonated polystyrene chains at 0.1-0.3 M concentrations,
498 our simulation results regarding our \mathbf{PSC}^{f_c} are in line with their experimental
499 conclusion^{11,54} : the \mathbf{PSC}^{f_c} gyration radius R_g depends increasingly on f_c .

500 In all our **P70** and \mathbf{PSC}^{f_c} simulations clearly show the variability of HPE
501 behaviors in water, behaviors that can not be modeled by considering only the
502 HPE charge fraction f_c . In the particular case of **P70**, we will discuss below another
503 pivotal parameter to understand HPE behaviors, *i.e.* the polarizability of the neutral
504 HPE moieties.

505 3.2 The collapsed conformations of P70 in the LRP medium

506 We performed a new set of 8 independent NVT simulations at the 10 ns scale of **P70**
507 surrounded by its counter ion cloud in the **LRP** medium. The simulation starting
508 structures correspond the final ones of the **SRP** simulations discussed above : the
509 first level box comprising **P70** in a CQS conformation, the counter ions and the
510 0.9M first level PPPs is embedded in a second level cubic box whose volume (about
511 216 nm³) is 8 times larger than the relaxed volume of the first level PPP box and

512 that is fulfilled by about 0.9M second level PPPs. The molecular size of that new
513 **LRP** system is thus equivalent to a 8M water molecules system.

514 3.2.1 Structural properties

515 In Fig. 8 we plot the temporal evolution of the **P70** gyration radius R_g along the
516 new simulations. These plots show a non-negligible and systematic contraction of R_g
517 along these simulations from 14.1 (**SRP**) to 12.4 (**LRP**) ± 0.1 Å. In **LRP**, the **P70**
518 CQS conformations are thus more compact than in **SRP**, by about 20 % in volume.
519 However, the most striking difference between **SRP** and **LRP** simulations concerns
520 the counter ion cloud. In Fig. 8 we plot the functions g_{ci} and $N_{ci}(r)$ computed
521 along the last 2 ns **LRP** simulation segments. If about 10 % of the counter ions are
522 adsorbed on the polymer surface as in **SRP**, only 24% of them now form a first shell
523 lying at the vicinity of the polymer surface (as in the **SRP** case) and 66% of them
524 form a second shell away from **P70** (it is centered at about 60 Å from PCOM).

525 Regarding first order PPPs, their structural features at the vicinity of the **P70**
526 surface are close to the **SRP** case, as well as their number trapped within the **P70**
527 CQS conformations (again about 270, see Fig. 4). In all the **P70** CQS conformations
528 are stable in **LRP**. However they are more contracted and their counter ion cloud
529 is strongly altered compared to **SRP**, with a large fraction of the counter ions lying
530 now away from **P70**.

531 3.2.2 Energies

532 The energy components $\Delta\bar{U}_p$, $\Delta\bar{U}_{ci}$, $\Delta\bar{U}_{pc}$, $\Delta\bar{U}_{ps}$ and $\Delta\bar{U}_{cs}$ computed along the last
533 2 ns segments of the **LRP** simulations are summarized in Tab. 1. As expected the
534 largest differences between **SRP** and **LRP** data arise from interactions involving
535 the counter ions and the PPPs. Because of the release of the counter ions away
536 from **P70**, the magnitude of the **P70**/counter ions interaction energy $\Delta\bar{U}_{pc}$ and of
537 the intra counter ion cloud energy $\Delta\bar{U}_{ci}$ decreases from **SRP** to **LRP** by about 90%

538 and 80 %, respectively. On the other hand long range solute/solvent interactions
539 strongly reinforce the stability of the polymer CQS conformations : the magnitudes
540 of $\Delta\bar{U}_{ps}$ and $\Delta\bar{U}_{cs}$ are from 3 to 4 times stronger along **LRP** simulations compared
541 to **SRP** ones, and that arises mainly from the second level PPPs.

542 From Eq. 7, we may estimate the order of magnitude of the hydration long range
543 electrostatic free energy ΔG_{lr} of a solute of charge Q (modeled as a point charge and
544 whose gyration radius is R_g) dissolved in a homogeneous second level PPPs shell
545 extending from $R_{cut}^{pol,1} + R_g$ to $R_{cut}^{pol,2}$ according to

$$\Delta G_{lr} = -\frac{\alpha_{s,2}}{2} \frac{Q^2}{4\pi\epsilon_0} \int_{R_{cut}^{pol,1} + R_g}^{R_{cut}^{pol,2}} \frac{\rho_s}{R^4} 4\pi R^2 dR = -\frac{Q^2}{8\pi\epsilon_0} \left(\frac{1}{R_{cut}^{pol,1} + R_g} - \frac{1}{R_{cut}^{pol,2}} \right). \quad (9)$$

546 For **P70** in a **SRP** CQS conformation, that yields $\Delta G_{lr} \approx -26 \cdot 10^3 \text{ kcal mol}^{-1}$,
547 a value in line with the $\Delta\bar{U}_{ps}$ data of Tab. 1. That relation can be readily rewritten
548 to estimate the hydration short range solute/solvent electrostatic free energy ΔG_{sr}
549 (arising from first level PPPs) as

$$\Delta G_{sr} = -\frac{Q^2}{8\pi\epsilon_0} \left(\frac{1}{R_g} - \frac{1}{R_{cut}^{pol,1} + R_g} \right). \quad (10)$$

550 These relations suggest that the more compact is a HPE CQS conformation
551 the stronger it is stabilized by both short and long range HPE/solvent electrostatic
552 interactions. For instance the gyration radius R_g smaller by 1.7 Å in **LRP** than
553 in **SRP** is responsible for an overall large decrease of ΔG_{sr} by about -5 700 kcal
554 mol⁻¹ according to the above relation. Within the **PPP^l** framework, long range
555 **P70**/solvent electrostatic effects favor the contraction of a CQS conformation and
556 thus the increase of the local charge densities within **P70**, a phenomenon which in
557 turn reinforces both the short and long range solvent/polymer electrostatic interac-
558 tions. However the contraction of a CQS conformation also yields to strengthen both
559 the intra HPE repulsive Coulombic and attractive polarization effects, by about 25

560 and 40 %, respectively (see Tab. 1).

561 We assess the stability of one of the final **LRP** CQS conformations by performing
562 a 500 *ns* simulation of it embedded together with its counter ion cloud in a first level
563 cubic box whose volume is 21.9 nm³ (and comprising about 80k first level PPPs), and
564 in a 8 times larger second level box (comprising also about 80k second level PPPs).
565 In that particular case $R_{\text{cut}}^{\text{pol},2}$ is 62.5 Å. We observe here also the **P70** structure to
566 jump among different CQS conformations whose structural and energetic properties
567 are close. In particular, their gyration radii are smaller than in **SRP** by about 1.7
568 Å, on average, see Fig. 5.

569 3.2.3 Second order PPPs and the distant counter ion shell

570 The **P70** PCOM/second order PPP radial distribution functions reported in Fig. 8
571 (d) show over concentration of second order PPPs in between **P70** and the distant
572 counter ion shell, a domain in which the electric field components generated by
573 opposite charged solutes are expected to be strong (whereas they mostly cancel
574 each other for like charged solutes, see Fig. 1 and Fig. 3-B). Hence the organized
575 **P70**/second order PPPs/counter ions shell structures observed at the end of our
576 **LRP** simulations yields to reinforce the polarization interactions among the second
577 order PPPs, **P70** and a set of counter ions. In our original study, we already showed
578 the density of second order PPPs to be slightly increased at the lower boundary of
579 their cut off shell domain³⁶ as they interact with a single monovalent ion like Cl⁻
580 or Na⁺. Here the large electrostatic charge of **P70** (and of its counter ions cloud)
581 yields to overestimate that phenomenon. In Section 4 we show how the decrease its
582 intensity by reinforcing the repulsion of second order PPPs at short range. However
583 even in that case the above conclusion regarding the stability and the contraction
584 (and its magnitude) of the **P70** CQS conformations arising from long range solvent
585 effects remains valid.

586 3.2.4 Comparison to carboxylated polystyrene PSC^{f_c}

587 We also simulated the carboxylated $\text{PSC}^{0.5}$ and PSC^1 in the **LRP** medium. The
588 linear PSC^{f_c} starting structures (comprising Na^+ counter ions) correspond to those
589 embedded in a 260k first order PPP box as detailed above. These hydrated structures
590 are here embedded in second order PPP boxes comprising also about 260k particles.
591 For each PSC^{f_c} we performed a single 100 ns MD simulations. Anticipating the
592 conclusions of Section 4, we set the parameter ϵ_2 to 1 kcal mol⁻¹. The temporal
593 evolutions of the gyration radii and the final snapshots at the end of these simulations
594 for both the PSC^{f_c} are provided as Supplementary Materials.

595 In **LRP**, the final conformation of PSC^1 is more elongated than in **SRP**: its
596 gyration radius R_g is 31 Å in **LRP**, larger by 41 % than in **SRP**. A weaker fraction
597 of counter ions Na^+ interact at short range from carboxylate heads in **LRP** than
598 in **SRP**: as stated in Ref.⁵⁴ that yields to strengthen the intra HPE destabilizing
599 forces arising from the Coulombic interactions among ionic heads and that explains
600 the more elongated conformation of PSC^1 in **LRP** than in **SRP**. Regarding $\text{PSC}^{0.5}$
601 its final conformation in **LRP** is also more elongated than in **SRP** ($R_g = 26$ Å) and
602 we note the formation of two "pearls" at both its extremities and whose cores are
603 stabilized by clusters of neutral phenyl groups. Such a conformation is in line with
604 the interpretation of experimental data provided in Ref.⁵⁴. As for PSC^1 a weaker
605 fraction of counter ions interact at short range from carboxylate heads in the final
606 conformation of $\text{PSC}^{0.5}$ in **LRP** than in **SRP**. That also favors its more elongated
607 conformation in **LRP**.

608 Hence our simulations show long range solvent effects to favor different kind of
609 HPE conformations : for **P70** they reinforce the stability of its CQS conformations
610 whereas for PSC^{f_c} with a high charge fraction ($f_c \geq 0.5$) they favor elongated
611 conformations. Hence our multi level PPP approach does not systematically favor
612 CQS-like conformations for highly charged HPEs.

613 3.3 Intra-polymer polarization

614 3.3.1 SRP medium

615 To further investigate the role of intra molecular polarization on **P70** conformations
616 solvated in a salt free **SRP** medium at infinite dilution conditions, we performed
617 two sets of 8 independent NVT simulations at the 10 *ns* scale of the **P70**/counter
618 ions system embedded in a 0.9 M first order PPPs cubic box, however by setting
619 to zero all the atomic polarizabilities. For these two simulation sets, their starting
620 structures correspond to those obtained at the end

- 621 1. of the initial 200 *ps* segments of the polarizable **P70** simulations in **SRP**, seg-
622 ments along which **P70** is harmonically constrained in its LSS conformation;
- 623 2. of the polarizable **P70** simulations in **SRP**, *i.e.* **P70** is in a CQS conformation.

624 These starting structures are relaxed by performing preliminary 200 *ps* NVT simu-
625 lations along which the **P70** structure is constrained and corresponding to different
626 starting velocity sets. The simulations are then restarted by removing the constraints
627 on **P70**.

628 In Fig. 9 we plot the temporal evolutions of the **P70** gyration radius R_g and ratio
629 R^{inertia} along both sets of simulations. As shown by these plots, the **P70** structures
630 converge within less than 8 *ns* towards quasi spherical conformations whose R_g value
631 is almost equal, about $21.5 \pm 1.0 \text{ \AA}$, regardless of the simulation starting structure.
632 These final conformations, denoted as QS^{nopol} , all present relatively large cavities
633 within them. Compared to the CQS conformations of polarizable **P70** in **SRP**, they
634 are less compact by a factor 3 in volume, and they correspond more to coil/helicoidal
635 conformations than to compact globular ones, see Fig. 2.

636 In Fig. 9 we also plot the **P70** $g_{\text{NN}}(r)$ and $N_{\text{Na}}(r)$, the counter ion $g_{\text{ci}}(r)$ and
637 $N_{\text{ci}}(r)$, and the solvent $g_{\text{PPP}}(r)$ and $N_{\text{PPP}}(r)$ functions computed along the last 2 *ns*
638 segments of the non-polarizable simulations. Regardless of the simulation starting

639 structure, the main features of the $g_{\text{NN}}(r)$ and $N_{\text{Na}}(r)$ functions are close. The
640 cationic charge distributions within all the QS^{nopol} conformations are thus close,
641 suggesting their main energetic properties to be also close (see below). We may also
642 note that, in line with the larger gyration radius of the QS^{nopol} conformations, the
643 present functions $g_{\text{NN}}(r)$ start to be non zero for inter nitrogen N_{a} distances r larger
644 by about 1.5 Å compared to their polarizable CQS counter parts, and they vanish
645 for distances r larger than 45 Å, *i.e.* 10 Å farther than for the polarizable CQs.

646 The counter ion $g_{\text{ci}}(r)$ and $N_{\text{ci}}(r)$ functions are also close, regardless of the start-
647 ing simulation structure. Contrary to the **SRP** simulations of polarizable **P70**, a
648 large fraction of the counter ions (about 20 %) is now adsorbed within the polymer
649 core and the remaining ones form a spherical shell centered at about 28 Å from
650 PCOM and extending up to about 18 Å from the **P70** 'surface' (*i.e.* the surface
651 of a sphere whose radius is R_g). Lastly, the solvent functions $g_{\text{PPP}}(r)$ show the first
652 level PPP density to be almost constant and to already reach 90% of its bulk value
653 within the **P70** core domain. That yields the hydration index (defined as the mean
654 number of first order PPPs lying within the **P70** core) of the QS^{nopol} conformations
655 to be 4 times larger than for CQS conformations (about 1200 and 270, respectively).
656 Hence the large cavities within the QS^{nopol} conformations are full filled by counter
657 ions and first level PPPs.

658 As expected from the close charge distributions within the QS^{nopol} conformations
659 and from the close counter ion and PPP structural properties, there are weak disper-
660 sions among the values of the mean energy components $\Delta\bar{U}_{\text{p}}$, $\Delta\bar{U}_{\text{ci}}$, $\Delta\bar{U}_{\text{pc}}$, $\Delta\bar{U}_{\text{ps}}$ and
661 $\Delta\bar{U}_{\text{cs}}$ computed along all the final 2 *ns* non-polarizable simulation segments. Com-
662 pared to polarizable data, the less compact QS^{nopol} conformations are tied to twice
663 weaker intra-**P70** Coulombic and **P70**/PPP interaction energies, see Tab. 1. Ac-
664 cording to Eqs. (9-10), the latter results may be interpreted as arising from the more
665 diluted cationic charge within the less compact QS^{nopol} conformations. Interestingly
666 the QS^{nopol} magnitudes of the mean intra counter ion cloud $\Delta\bar{U}_{\text{ci}}$, **P70**/counter ions

667 $\Delta\bar{U}_{pc}$ and counter ions/solvent energies $\Delta\bar{U}_{cs}$ agree with the CQS one.

668 3.3.2 LRP medium

669 We performed a new set of 8 independent NVT simulations in **LRP** whose starting
670 **P70**/counter ions structures correspond to the final ones of the non-polarizable
671 simulations in **SRP**. However these structures are embedded in two 0.9M first and
672 second level PPP cubic boxes and they are simulated at the 20 *ns* scale. As above all
673 the **P70** atomic polarizabilities are zeroed. The main **P70**, counter ions and solvent
674 structural and energetic data, averaged over the last 2 *ns* simulation segments, are
675 reported in Fig. 10 and in Tab. 1.

676 Accounting for second level PPPs, and thus for long range solvent electrostatic
677 effects, yields again (1) a large fraction of the counter ions to be largely repelled away
678 from **P70** (they form again a distant shell lying at about 50-60 Å from PCOM), and
679 (2) a strong contraction of the starting QS^{nopol} conformations : their mean gyration
680 radius R_g decrease from 21.5 ± 1 Å in **SRP** towards 14.2 ± 0.2 Å in **LRP**. The struc-
681 tural details of these new **LRP** compact and quasi spherical conformations, denoted
682 as CQS^{nopol} , are overall close to the CQS ones corresponding to polarizable **P70** in
683 **SRP**, see Fig. 10(b). However, regarding the counter ions, the noticeable fraction of
684 them (about 20%) that were trapped within the starting QS^{nopol} conformations are
685 still trapped within the final CQS^{nopol} ones. All these results may be interpreted as
686 above for the polarizable **P70** embedded in the **LRP** medium. However the large
687 fraction of the counter ions trapped within the CQS^{nopol} final conformations are re-
688 sponsible for a strong HPE discharging effect that stabilizes these conformations as
689 intra-**P70** polarization attractive forces favor CQS conformations.

690 As for polarizable **P70**, the **P70**/counter ion radial distribution functions re-
691 ported in Fig. 10 show here also the existence of a distant counter ion shell lying at
692 60 Å from PCOM. As discussed for polarizable **P70**, the origin of that shell arises
693 here also from over concentration of second order PPPs in between that shell and

694 **P70**. As it will be discussed in Section 4, reinforcing the short repulsion among
695 second order PPPs will yield that distant shell to vanish. However that will not lead
696 to invalidate the present conclusions about the contraction of the non polarizable
697 **P70** conformations arising from long range solvent effects.

698 At the exception of polarization and counter ion energy data, the energetic data
699 reported in Tab. 1 for non-polarizable **P70** in **LRP** are in line with their polariz-
700 able **P70** counter parts. In particular we note again the strong stabilization of the
701 CQS^{nopol} conformations arising from long range solvent electrostatic effects. Regard-
702 ing counter ions, long range solvent electrostatic effects favors their structure as for
703 polarizable **P70**, but more strongly as suggested by the magnitude of the energy
704 component $\Delta\bar{U}_{cs}$. As that component only measures the strength of the counter
705 ion/solvent interaction, its strong intensity here may result from the large fraction
706 of counter ions trapped within the overall small volume corresponding to CQS^{nopol}
707 conformations, as suggested by Eqs. 9 and 10.

708 Besides confirming the role of electrostatic long range solvent effects, our non-
709 polarizable **P70** simulations clearly show the strong effect of intra-molecular polar-
710 ization on the conformation of a HPE in liquid water-like **SRP** and **LRP** media.
711 According to our modeling framework, these intra-molecular polarization effects are
712 not tied to the strongest interaction energies within our HPE/counter ions/solvent
713 systems, but they are a key factor favoring HPE compact globular conformations.

714 4 HPE collapse and the solvent coarse grained ap- 715 proach

716 Coarse-graining the solvent yields approximations in modeling solute/solvent inter-
717 actions. As even conclusions from all atom simulations regarding the association
718 of standard ion pairs in aqueous phase vary noticeably when considering different
719 sets of all atom force field parameters⁷¹⁻⁷³, one may wonder about the reliability of

720 simulations based on a solvent coarse grained approach to investigate the behavior
721 of a heavily charged HPE like **P70**.

722 In an earlier study³⁷, we showed the **PPP**^{*l*} approach to meet the predictions of
723 the lattice numerical method implemented in the APBS code⁷⁴ to solve the Poisson
724 Boltzman equations as computing the electrostatic component of the hydration free
725 energy of proteins, a particular kind of polyelectrolytes. Here we further investigate
726 the **PPP**^{*l*} accuracy by performing an additional set of eight simulations of **P70**
727 embedded in 1M first level PPP box. These simulations correspond to polarizability
728 values α_s of the PPPs that range from 1.2 up 2.7 \AA^3 (the α_s value computed from
729 Equation (4) is 2.35 \AA^3). Each simulation was performed as detailed above up to
730 10 ns from the **P70** linear starting structure. In Fig. 11 we plot the mean **P70**
731 gyration radius R_g and the mean **P70**/solvent interaction energy U_{ps} as a function
732 of α_s (these mean quantities are computed over the final simulation segment on
733 which the **P70** structure is stable). From these plots it appears that **P70** collapses
734 within 10 ns towards a CQS conformation as soon as $\alpha_s = 1.8 \text{\AA}^3$, a value 30%
735 smaller than the one we used in the above simulations. Regarding the U_{ps} values,
736 their magnitude for the **P70** CQS conformation is a decreasing linear function of α_s
737 : it ranges from -20 ($\alpha_s = 1.8 \text{\AA}^3$) down to -39 ($\alpha_s = 2.7 \text{\AA}^3$) $10^3 \text{ kcal mol}^{-1}$.

738 We simulated **P70** in its CQS conformation as embedded in a spherical cavity
739 whose radius is 43 \AA and comprising about 7 500 explicit and polarizable water
740 molecules. **P70** and water were simulated using an all atom polarizable force field
741 whose accuracy is discussed in Refs.^{56,75} (see also Supplementary Material for de-
742 tails). That all atom simulation yields a U_{ps} value that ranges from -26 to -28 10^3
743 kcal mol^{-1} as accounting for water molecules lying within a shell extending up to
744 12 \AA from the **P70** boundary (as defined in Section 2.3). Such a U_{ps} value is fully
745 in line with our **PPP**^{*l*} estimate for $\alpha_s = 2.35 \text{\AA}^3$.

746 Defining HPE structures by analogy with proteins, the secondary structure of
747 **P70** for low values α_s (up to 1.8 \AA^3) corresponds to long helices where the ammo-

748 nium groups point towards the solvent and they interact at short range with the
749 counter ions. These helices can adopt neck-lace, wormlike or more compact folded
750 conformations (see Supplementary Material) showing the wide range of potential
751 **P70** tertiary structures in low to moderately polarizable solvents. For instance the
752 **P70** tertiary structure along our simulations is a neck lace for $\alpha_s = 1.2 \text{ \AA}^3$ and
753 wormlike for $\alpha_s = 1.4 \text{ \AA}^3$ (that explains their respective gyration radius values in
754 Fig. 11). However both kind of structures are very close in energy, regardless of the
755 latter α_s values.

756 For large α_s values, the helix secondary structure vanishes and **P70** collapses
757 towards more disordered, compact and quasi spherical conformations as discussed
758 in the above section. Around these CQS conformations we note the counter ions to
759 form a more and more diffuse cloud that extends farther and farther from the **P70**
760 boundary as α_s increases. Whereas salts were considered as fully dissociated in water
761 at low to moderate concentrations, large salt/water aggregates are now inferred to
762 be abundant even in dilute solutions^{76–79}. The stability of such edifices may be
763 explained from similar arguments as those schematized in Fig. 1(b) : the stability
764 of polarizable water molecules intercalated between two species of opposite charges
765 is reinforced by the resulting non zero electric field generated by the latter charges
766 on them. These effects are responsible for the stability of the well known Solvent
767 Separated Ion Pair, SSIP, conformations that are pivotal in the ion pair dissociation
768 process in aqueous phase (see Ref.⁸⁰ and the references mentioned therein). Our
769 hybrid simulations show SSIP-like **P70**/counter ions to be more and more favored
770 as α_s increases.

771 Lastly we have to take in mind that our simulations are performed in infinite di-
772 lution conditions. The HPE solutions that are experimentally investigated comprise
773 an overall large number of HPE chains, each of them generating local electric fields
774 on the solvent. Even if these fields undergo large fluctuations, they will on average
775 less polarize the solvent located in between two HPE chains than the solvent lying

776 at the vicinity of a single and isolated HPE chain as in the present study. That
777 arises from the electric field cancellation effect detailed in Fig. 1(b) (that effect is
778 thus opposite to the above one favoring SSIP-like conformations). Hence within
779 our **PPP**^l framework, increasing the concentration of HPE is expected to weaken
780 HPE/solvent interactions and thus to destabilize HPE CQS conformations and to
781 favor more elongated HPE ones.

782 Regarding second order PPPs and the magnitude of the ϵ_2 parameter modulating
783 the intensity of the LJ interactions among them, we performed two new series of
784 eight MD simulations by considering **P70** as a polarizable and a non polarizable
785 entity. Instead of using a parameter ϵ_2 one order of magnitude smaller than the
786 one used for first level PPPs (*i.e.* $\epsilon_2 = 0.05$ kcal mol⁻¹), we set ϵ_2 to a value
787 ranging from 1 to 8 kcal mol⁻¹ to perform these new simulations. Besides reinforcing
788 the interactions among second order PPPs, these larger ϵ_2 values also noticeably
789 reinforce the strength of the short range repulsion among second order PPPs (see
790 Supporting Material). That will thus prevent (at least in part) over concentration
791 of second order PPPs at the vicinity of charged solutes. The **P70** starting structure
792 (and its counter ion cloud) correspond to one of the final CQS conformations of a
793 polarizable simulation in **SRP**. That structure is embedded in a first order PPP
794 box whose dimension is 200 Å. That yields a system comprising about 260k first
795 order PPPs that is embedded in a second order PPP box comprising also about
796 260k particles. The simulations were performed as detailed above up to 30 ns. The
797 ion/**P70** PCOM radial distribution functions $g_{ci}(r)$ and their integrals $N_{ci}(r)$ are
798 provided as Supplementary Material. These functions show a large fraction of the
799 counter ions to not be any more organized as a distant shell lying at about 60 Å
800 from the **P70** PCOM, but rather to belong to a diffuse counter ion cloud extending
801 within the entire simulation box. That behavior is observed for any value of $\epsilon_2 \geq 1$
802 kcal mol⁻¹. Regarding polarizable **P70**, its CQS conformation is stable and still
803 more contracted as compared to simulations in **SRP** (the **P70** gyration radii at

804 the end of these new simulations are weaker by 0.6 to 1.5 Å than in **SRP**). For
805 non polarizable **P70**, its structure is also more contracted than in **SRP** (the **P70**
806 gyration radii range from 15 to 18 Å). For both polarizable and non polarizable
807 **P70**, we do not observe a dependence of their gyration radius on the magnitude of
808 $\epsilon_2 \geq 1$ kcal mol⁻¹. Hence, even if there is room to improve the modeling of inter
809 particle interactions for high order PPPs, all our results show solvent long range
810 effects (as modeled by our second order PPPs) to reinforce the stability of the **P70**
811 CQS conformations and to favor more contracted CQS conformations than do only
812 short range solvent effects.

813 In all the above discussions suggest our **PPP^l** approach to capture the main
814 effects regarding HPE hydration. In particular our hybrid approach does not over-
815 estimate the solute/solvent interactions that stabilize CQS-like HPE conformations
816 in the present study. It is thus a priori able to provide reliable quantitative conclu-
817 sions regarding the behavior of HPEs in aqueous phase. However and contrary to
818 our original study³⁶ we recommend the use of large LJ ϵ_k parameters (*i.e.* $\epsilon_k \geq 1$
819 kcal mol⁻¹) to model the interactions among PPPs whose order k is higher than
820 one.

821 5 Conclusion

822 We presented MD simulation results about the HPE **P70** solvated in salt free liquid
823 water-like **SRP** and **LRP** media, in presence of counter ions and at infinite dilution
824 conditions. The **SRP** and **LRP** media are modeled by means of polarizable particles
825 PPPs according to the multi-level CG **PPP^l** approach. In the **SRP** medium, only
826 PPPs whose size matches that of a single water molecule are taken into account
827 and they interact with the solutes if they lie within a shell extending to no more
828 than 12 Å from any solute non hydrogen atom. For the **LRP** medium, we take into
829 account these first level PPPs as well as a new set of larger PPPs (whose volume

830 is 8 times larger than that of a single water molecule) that interact only with the
831 HPE charged groups and the counter ions if they lie within 12 to 143 Å from the
832 solutes. The two regimes behavior of the free energy corresponding to the creation
833 of an empty cavity within liquid water (as predicted by to the Lum-Chandler-Weeks
834 theory of hydrophobicity⁶²) is reproduced by these two media. The properties of the
835 **LRP** medium are close to the liquid water one³⁶ whereas the **SRP** medium may
836 be interpreted as the solvent water confined in a cavity. The HPE and its counter
837 ion cloud are taken into account explicitly and modeled according to the *all atom*
838 polarizable force field TCPEp approach³¹.

839 From a **P70** linear starting structure surrounded by a thin layer of counter ions,
840 we performed multiple simulations of that system embedded in the **SRP** medium
841 modeled as a cubic box comprising about 0.9 M first level PPPs (and whose volume
842 is 27 nm³). Our simulations show **P70** to collapse in that medium towards compact
843 and quasi-spherical conformations surrounded by a counter ion shell lying a short
844 range (about 8-10 Å) from the **P70** surface. Even if the atomic details of these con-
845 formations differ among the simulations, the spatial distributions of their cationic
846 groups are close suggesting these conformations to be close in energy in **SRP** as
847 supported by the analysis of different energy components performed along the simu-
848 lations, like intra-**P70** and **P70**/counter ions interaction energies. The **P70** compact
849 and quasi spherical conformations relaxed in the **SRP** medium were then simulated
850 in the **LRP** medium by embedding the final structures of the **P70**/counter ions/0.9
851 M first level PPPs systems in a new cubic box comprising 0.9 M second level PPPs
852 and whose volume is 216 nm³. That new system accounts thus for an equivalent
853 of 8M water molecules. The **SRP** compact and quasi spherical conformations are
854 structurally stable in **LRP**, even if we note a noticeable contraction of them (by
855 about 20 % in volume) as well as a large fraction of the counter ions to be repelled
856 at farther distances from **P70** than in **SRP**. Both the latter results arise from long
857 range solvent electrostatic effects that weakens the association of oppositely charged

858 systems and favors the contraction of heavy charged flexible solutes.

859 For comparison purposes we also simulated at the 100 ns scale four carboxylated
860 polystyrenes \mathbf{PSC}^{f_c} (whose fraction of charge varies from 0 to 1) in both the **SRP**
861 and the **LRP** medium by means of our MD protocol. These HPEs are shown by
862 our simulations to behave as the sulfonated polystyrenes experimentally investigated
863 by Boué and co workers^{11,54} : their gyration radius increases as their charge frac-
864 tion increases. In particular and contrary to our **P70**, the fully carboxylated \mathbf{PSC}^1
865 evolves along a 100 ns MD trajectory towards a helicoidal structure in **SRP** (struc-
866 ture that is stabilized by local carboxylate/counter ion salt bridges) and towards a
867 more elongated structure in **LRP**.

868 Even if the behavior of **P70** in our water-like **SRP** and **LRP** media does not pre-
869 judge of the behavior of any kind of HPEs in such environments (in particular their
870 collapse towards compact conformations as discussed for carboxylated polystyrenes
871 \mathbf{PSC}^{f_c} with a high charge fraction) we may draw general conclusions from our sim-
872 ulations. The behavior of a HPE in any solvent is governed by a complex interplay
873 among microscopic interactions occurring within it and between the HPE and its
874 environment (counter ions and solvent). In particular, in salt free solutions and at
875 infinite dilution conditions, our simulations show that

- 876 1. in line with the standard picture of the effects governing the behavior of a HPE
877 in solution (see Ref.⁸¹ for instance), HPE compact conformations are disfa-
878 vored by strong Coulombic intra HPE effects and favored by strong Coulombic
879 HPE/counter ions ones, especially in a **SRP** medium in which the association
880 of oppositely charged ions is more favored than in **LRP**;
- 881 2. solute/solvent electrostatic interactions (as described within the \mathbf{PPP}^l frame-
882 work) and particularly long range ones, favor HPE compact conformations :
883 that yields the reinforcement of the HPE local density of charge which in turn
884 strengthens the electrostatic response of a polarizable solvent like water to the

885 HPE presence;

886 3. the existence of strong intra HPE attractive polarization effects (arising from
887 the polarization of alkyl carbons by the HPE ionic charges, for instance) also
888 favors HPE compact conformations.

889 We also simulated a non-polarizable **P70** in both the **SRP** and **LRP** media.
890 These new simulations support the key role played by intra HPE polarization effects
891 to understand the stability of HPE compact globular conformations as in the partic-
892 ular case of **P70**. Not accounting for them in our simulations yields **P70** to adopt
893 less compact conformations : their gyration radii increase by a factor of about 50%
894 (**SRP**) and 20% (**LRP**) compared to the compact structures predicted by account-
895 ing for these polarization effects. In the present case, intra HPE polarization effects
896 correspond to attractive forces. They may thus be modeled using a basic additive
897 dispersion-like energy term. However polarization is a non-linear phenomenon that
898 can be attractive, repulsive and even vanish for particular molecular geometries,
899 and might be extremely relevant for studying Natural ingredients like polysaccha-
900 rides as already shown for polypeptides. Hence microscopic polarization has to be
901 explicitly taken into account not only to model HPE systems at infinite dilution
902 conditions (as in the present study) but also in more complex and concentrated
903 chemical environments for which it is not obvious to infer the role of polarization
904 (like to favor/disfavor short range interactions among HPEs for instance). Our works
905 emphasizes the importance of considering polarizability for the future of digitally-
906 enabled formulation for Green Sciences. Lastly our hybrid modeling approach is
907 well suited to be used in conjunction with efficient algorithms to simulate explicitly
908 very large solutes (or mixtures of solutes), like a Fast Multipole Method devoted to
909 induced dipole-based polarizable force fields.⁸²

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912 2019-2020 [x2016081859] and the Grand Challenge allocation [GC0429] made by
913 GENCI.

914 Data Availability

915 Data openly available in a public repository that does not issue DOIs. A full binary
916 version of our simulation code POLARIS(MD) (version 1.2.0.1) and the input files
917 that were used for the present study to perform simulations on a multi core processor
918 are freely available for download⁶⁴.

919 Supplementary Material

920 See supplementary material for the details regarding (1) the all atom simulation of
921 **P70** embedded in an aqueous cavity and the its final conformations as a function
922 of the solvent polarizability; (2) the simulation data of the **PSC^{fc}** in the **SRP**
923 and **LRP** media; (3) the simulation data of **P70** in **LRP** using a LJ parameter
924 ϵ_2 ranging from 1 to 8 kcal mol⁻¹. A short video is also provided that shows the
925 collapse of the polyelectrolyte along a simulation in the 1M first level pseudo particle
926 box.

927 Conflicts of interest

928 A. C. and F. L. are full employees of L'Oréal involved in research activities.

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Table 1: Decomposition in Coulombic $\Delta\bar{U}^{qq}$, polarization $\Delta\bar{U}^{pol}$ and non electrostatic $\Delta\bar{U}^{ne}$ energy components of the intra-**P70** and intra-counter ion cloud mean energies $\Delta\bar{U}_p$ and $\Delta\bar{U}_{ci}$ and of the **P70**/counter ions, **P70**/PPPs and counter ions/PPPs interaction energies $\Delta\bar{U}_{pc}$, $\Delta\bar{U}_{ps}$ and $\Delta\bar{U}_{cs}$. Data in italic correspond to the root mean square deviations of these values among the independent simulations. For **LRP**, the $\Delta\bar{U}_{ps}$ and $\Delta\bar{U}_{cs}$ data in brackets corresponds to the first level PPP contributions. The non electrostatic component $\Delta\bar{U}^{ne}$ corresponds to the energy terms U^{disp}/U^{coop} or to the PPP/solute Lennard-Jones-like term (see Section 2). All values are expressed in 10^3 kcal mol $^{-1}$. Values smaller than 100 kcal mol $^{-1}$ are not reported.

	$\Delta\bar{U}^{qq}$	$\Delta\bar{U}^{pol}$	$\Delta\bar{U}^{ne}$
SRP	medium and polarizable P70		
$\Delta\bar{U}_p$	23.9 <i>0.4</i>	-2.6 <i>0.1</i>	-0.3 <i>0.02</i>
$\Delta\bar{U}_{ci}$	9.8 <i>0.4</i>	-0.1 <i>0.02</i>	
$\Delta\bar{U}_{pc}$	-24.1 <i>0.6</i>		0.1 <i>0.05</i>
$\Delta\bar{U}_{ps}$		-11.6 <i>0.3</i>	0.1 <i>0.05</i>
$\Delta\bar{U}_{cs}$		-3.2 <i>0.1</i>	
LRP	medium and polarizable P70		
$\Delta\bar{U}_p$	30.2 <i>0.6</i>	-4.6 <i>0.3</i>	-0.8 <i>0.1</i>
$\Delta\bar{U}_{ci}$	2.4 <i>1.3</i>		0.1 <i>0.05</i>
$\Delta\bar{U}_{pc}$	-2.8 <i>1.6</i>	0.3 <i>0.1</i>	
$\Delta\bar{U}_{ps}$		-52.8 <i>2</i> [-15 <i>0.3</i>]	0.6 <i>11</i>
$\Delta\bar{U}_{cs}$		-13.8 <i>14</i> [-9.3 <i>1.8</i>]	
SRP	medium and non polarizable P70		
$\Delta\bar{U}_p$	11.9 <i>0.3</i>		
$\Delta\bar{U}_{ci}$	10.4 <i>0.3</i>		
$\Delta\bar{U}_{pc}$	-23.8 <i>0.7</i>		
$\Delta\bar{U}_{ps}$		-5.1 <i>0.2</i>	-0.1
$\Delta\bar{U}_{cs}$		-3.9 <i>0.1</i>	
LRP	medium and non polarizable P70		
$\Delta\bar{U}_p$	30.3 <i>0.5</i>		-0.5 <i>0.1</i>
$\Delta\bar{U}_{ci}$	14.5 <i>4.8</i>		
$\Delta\bar{U}_{pc}$	-5.8 <i>3.2</i>	0.1 <i>0.02</i>	-0.1 <i>0.02</i>
$\Delta\bar{U}_{ps}$		-52.5 <i>1.5</i> [-10.3 <i>0.3</i>]	0.8 <i>0.1</i>
$\Delta\bar{U}_{cs}$		-31.8 <i>7.7</i> [-7.7 <i>1.9</i>]	0.2 <i>0.01</i>

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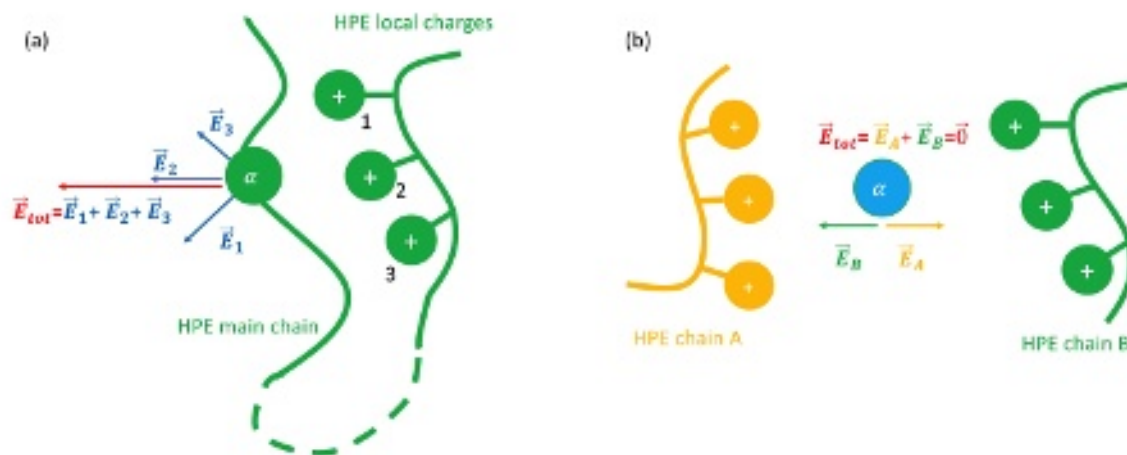


Figure 1: Microscopic polarization effects. (a) An atom, whose isotropic polarizability is α , belonging to a HPE (in green) is located at the vicinity of three positively charged groups. All the other atoms are non-polarizable centers. That atom undergoes the total electric field $\mathbf{E}_{tot} = \mathbf{E}_1 + \mathbf{E}_2 + \mathbf{E}_3$ arising from the three positive charges. From an induced dipole moment approach, the dipole moment generated on that atom obeys $\alpha\mathbf{E}_{tot}$ and it is at the origin of non additive polarization energy component $-\frac{1}{2}\alpha\mathbf{E}_{tot}^2$ that can not be modeled using standard additive potentials. (b) A solvent molecule whose polarizability is α is located in between two HPE chains A and B. The electric fields arising from each chain cancel out. If the charges of chain A are opposite to those of chain B, then the resulting electric field on the solvent is $\mathbf{E}_{tot} = \mathbf{E}_A + \mathbf{E}_B = 2\mathbf{E}_A = 2\mathbf{E}_B \neq \mathbf{0}$, and the corresponding polarization energy on the solvent is four times greater than as arising from each single chain taken alone.

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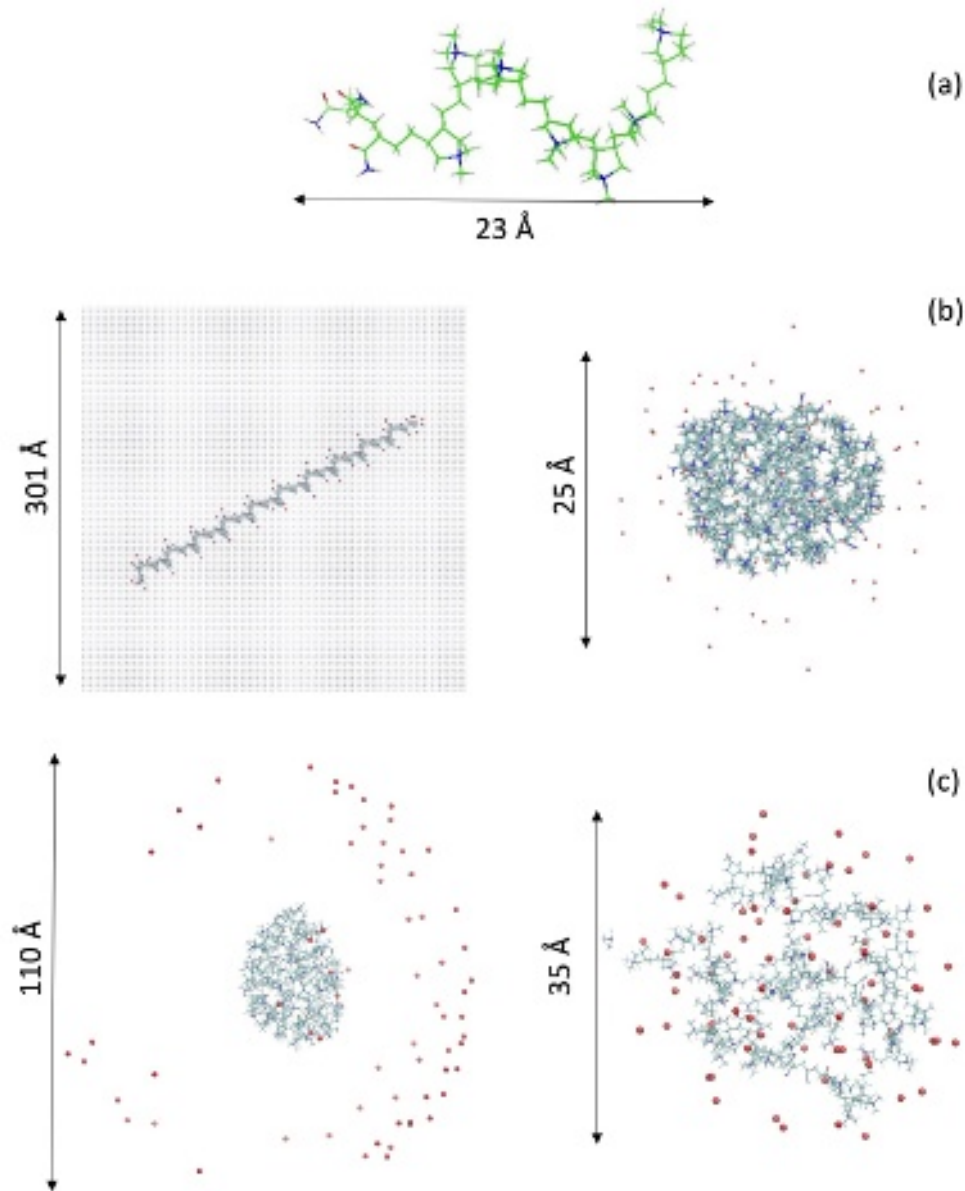


Figure 2: (a) A three dimensional representation of the main **P70** unit of the modeled, generic, HPE copolymer. The HPE is made of 10 units each comprising 7 adjacent cyclo butyl ammonium cationic heads interconnect by ethyl groups, that are connected to 3 more adjacent neutral groups equivalent to a triade of asparagine proteinic residues³⁸⁻⁴². The HPE total charge is thus $+70 e$. Here the carbon, hydrogen, nitrogen and oxygen atoms are shown in light blue, grey, dark blue and red. (b) Left : **P70** in its LSS conformation embedded in a 0.9M PPPs cubic box and whose electrostatic charge is neutralized by 70 Cl^- counter ions (in red, PPPs are shown in blue). Right : a CQS conformation of **P70** in the **SRP** medium. (c) Left : a CQS conformation of **P70** in the **LRP** medium. Right : an inflated conformation of the non polarizable **P70** in the **SRP** medium.

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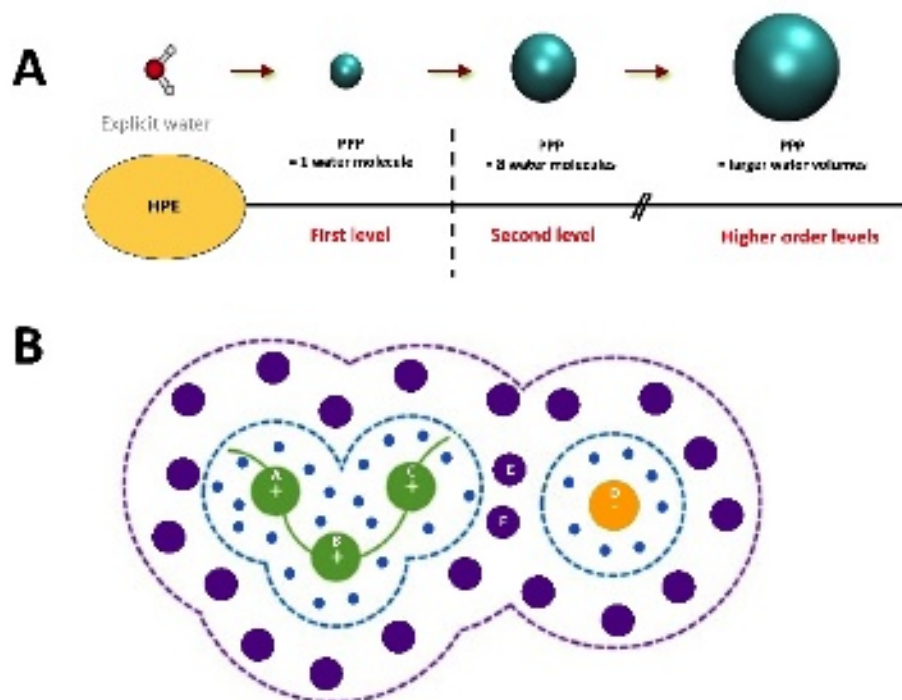


Figure 3: A The multi-level solvent CG approach \mathbf{PPP}^l . The blue spheres are PPP particles that differ by their size and thus by their polarizability. The vertical line correspond to the cutoff distance $R_{\text{cut}}^{\text{pol}}$ mentioned in the text. Smooth transitions exist between the different PPP level shells, *i.e.* the PPP/HPE interactions are scaled by B-spline functions that smoothly vary between 1 and 0 (lower PPP level) and between 0 and 1 (higher PPP level) at solvent shell boundaries. B Example of a HPE (in green) interacting with a counter ion D (in orange) solvated by first (in blue) and second order (in violet) PPPs. The dashed lines defined the first and second order shell-based cut off domains. Any first level PPP located within the domain delimited by the blue dashed lines undergoes the total electric field generated by all the HPE and counter ion charges (denoted here as A, B, C and D). Any second level PPPs located within the domain delimited by the blue and the violet dashed lines also undergoes the latter electric field.

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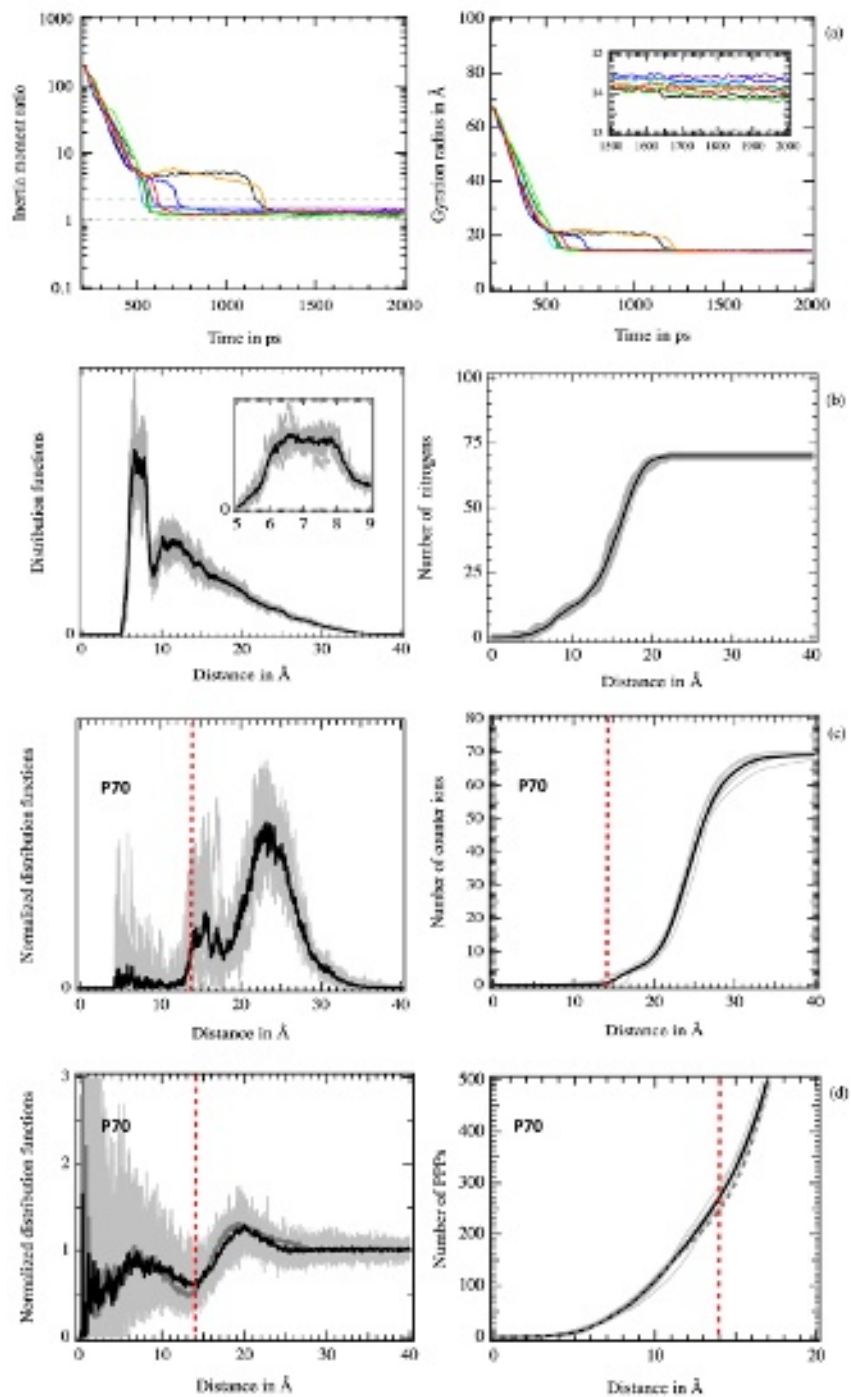


Figure 4: (a) Right : temporal evolution of the ratio between the smallest and largest inertia moment values (left) and of the gyration radius (right) of **P70** along the independent simulations in the **SRP** medium. (b) Mean radial pair distribution function \bar{g}_{NN} (left, the inset shows the details of its first peak) and mean number $\bar{N}(N_a)$ (right). (c) Mean radial distribution function $\bar{g}_{ci}(r)$ (left) and its corresponding integral $N_{ci}(r)$ (right). (d) Mean radial PPP/PCOM distribution function (left) and its corresponding integral (right). From (b) and (d) : the data from each independent simulation are shown by grey lines. The vertical dashed red line is located at the converged **P70** mean gyration radius.

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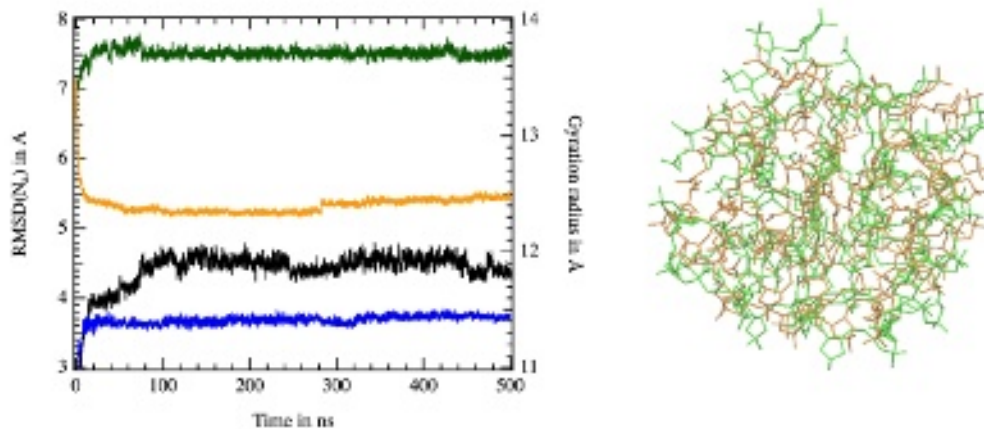


Figure 5: Left : temporal evolution of the **P70** RMSD(N_a) (left axis) and gyration radius (right axis) along the 500 *ns* simulations. Black (**SRP**) and blue (**LRP**) lines : RMSD(N_a) data. Green (**SRP**) and orange (**LRP**) lines : gyration radius data. Right : superposition of the starting (green) and final (orange) **P70** CQS structures from the 500 *ns* **SRP** simulation.

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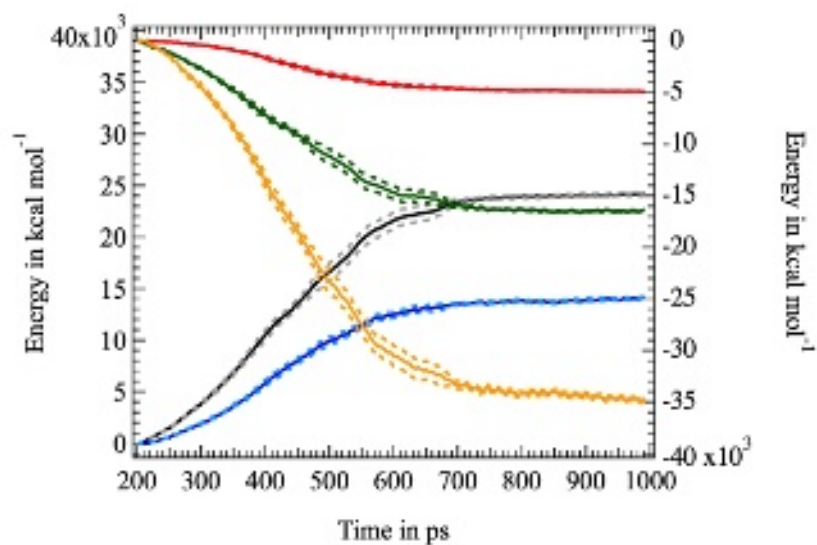


Figure 6: Temporal evolution of the energy component values computed by averaging data from all the independent simulations in the **SRP** medium, in bold lines. In dashed lines, the maximum deviations from the mean data. Black and blue : intra-**P70** and intra-counter ion cloud interaction energies (left axis) ; red, green and yellow : **P70**/PPPs and counter ions/PPPs polarization energies, and **P70**/counter ions interaction energy, respectively (right axis). All the energy components are shifted to be zero at simulation time $t = 200$ ps at which the harmonic constraints preventing **P70** structural transitions are removed.

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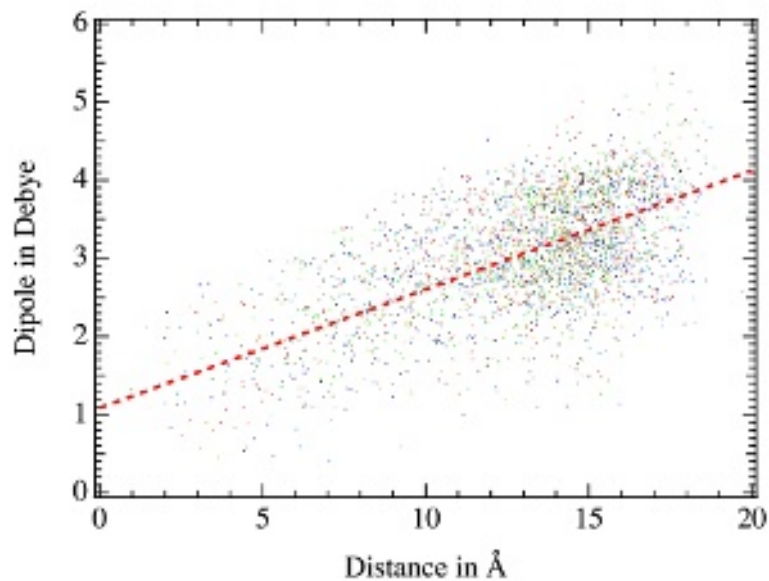


Figure 7: Mean induced dipole moment values of the **P70** alkyl carbons computed along all the independent simulations as a function of the alkyl carbon distance to PCOM. The dashed line is the result of the linear regression fit (the regression coefficient is here of 0.6).

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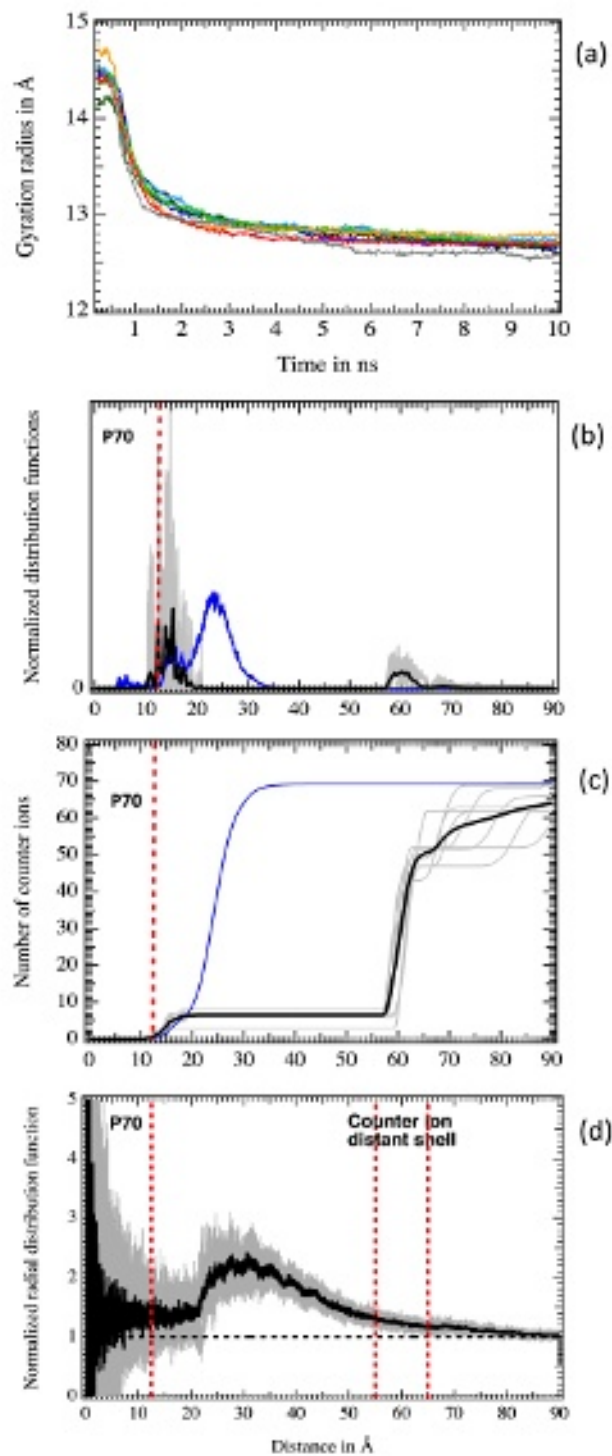


Figure 8: CQS **P70** and counter ion structural data in a **LRP** medium. (a) Temporal evolution of the **P70** gyration radius R_g along the independent simulations. (b) and (c) : counter ion functions $g_{ci}(r)$ and $N_{ci}(r)$, respectively (black line : mean functions averaged over all the simulations; grey lines : data from each simulation ; blue thin lines : mean functions from **P70 SRP** simulations; the vertical red line is located at the mean **P70** gyration radius R_g). (d) : **P70** PCOM/second order PPPs radial distribution functions from the independent simulations (in light grey lines) and the corresponding mean function (bold black line).

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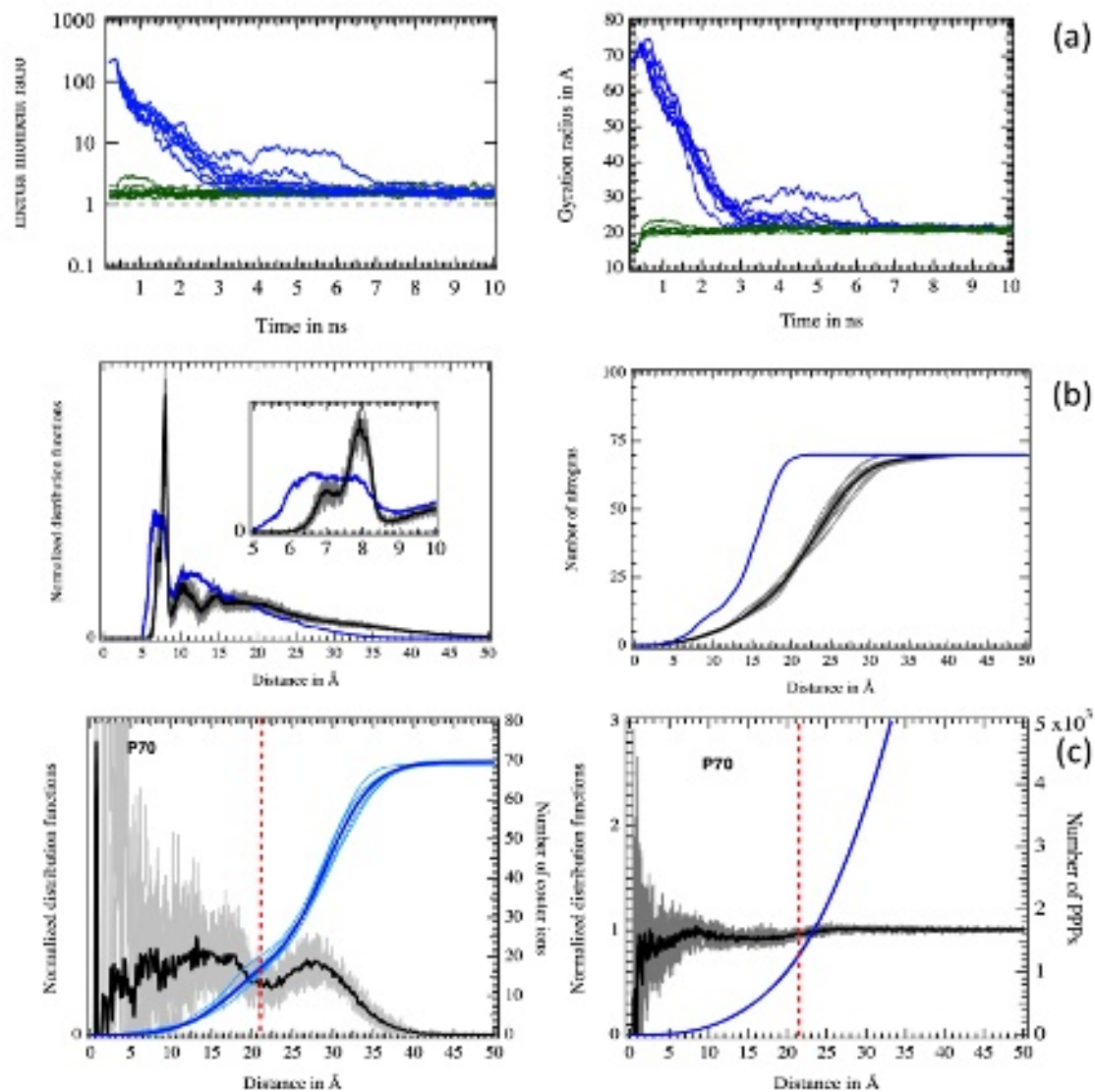


Figure 9: **P70**, counter ion and PPP structural data from non-polarizable **P70** simulations in the **SRP** medium. (a) Temporal evolution of the **P70** ratio R_{inertia} (left) and gyration radius R_g (right). Blue data : from the starting LSS structure; green data : from the starting CQS one. (b) Functions $g_{\text{NN}}(r)$ (left) and $N_{\text{Na}}(r)$ (right). Black line : data averaged over all the simulations; grey lines : data from each single simulation ; blue line : mean functions from polarizable **P70** simulations in **SRP**. (c) Left : Counter ion functions $g_{\text{ci}}(r)$ (black) and $N_{\text{ci}}(r)$ (blue), and right : PPP functions $g_{\text{PPP}}(r)$ (black) and $N_{\text{PPP}}(r)$ (blue). Bold lines : data averaged over all the simulations; thin lines : data from each simulation. The vertical red line is located at the mean **P70** gyration radius R_g .

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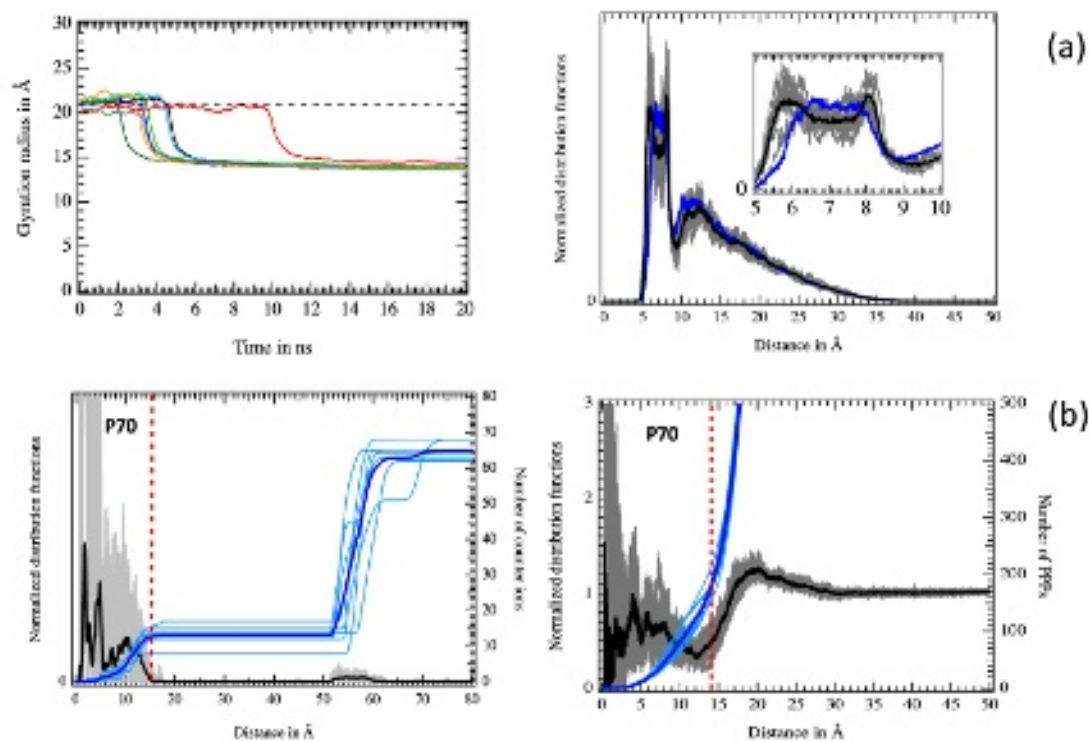


Figure 10: **P70**, counter ion and PPP structural data from non-polarizable **P70** simulations in the **LRP** medium. (a) Left : temporal evolution of the **P70** gyration radius R_g (the horizontal dashed line is located at the non-polarizable **P70** gyration radius converged value in **SRP**). Right : functions $g_{NN}(r)$ (black line : data averaged over all the **LRP** simulations; grey lines : data from each single **LRP** simulation; blue line : data averaged over the polarizable **P70** simulations in **SRP**). (b) Left : counter ion functions $g_{ci}(r)$ (black) and $N_{ci}(r)$ (blue). Right : PPP functions $g_{PPP}(r)$ (black) and $N_{PPP}(r)$ (blue). Bold lines : data averaged over all the simulations; thin lines : data from each simulation. The vertical red line is located at the mean **P70** gyration radius R_g .

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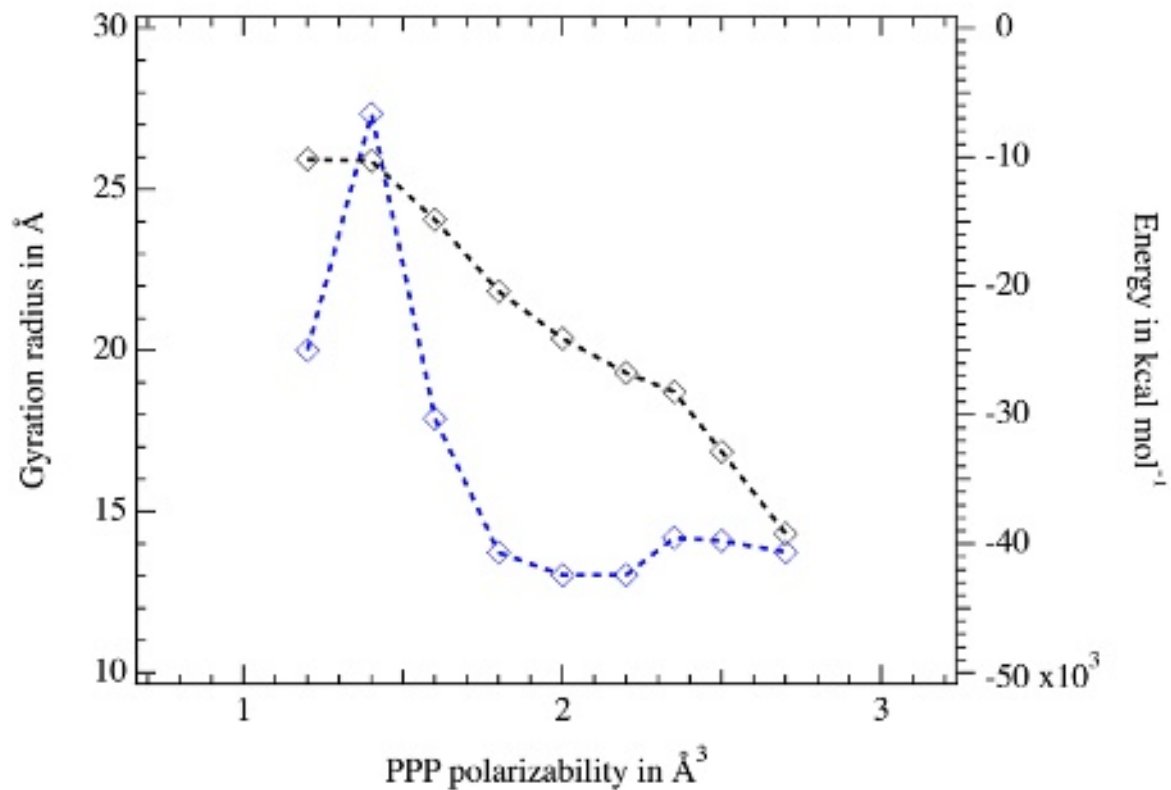


Figure 11: Mean **P70** gyration radius R_g (in blue and left axis) and mean **P70**/solvent interaction energy U_{ps} (in black and right axis) as a function of the PPP polarizability α_s . That polarizability amounts to 2.35 \AA^3 according to Equation (4).

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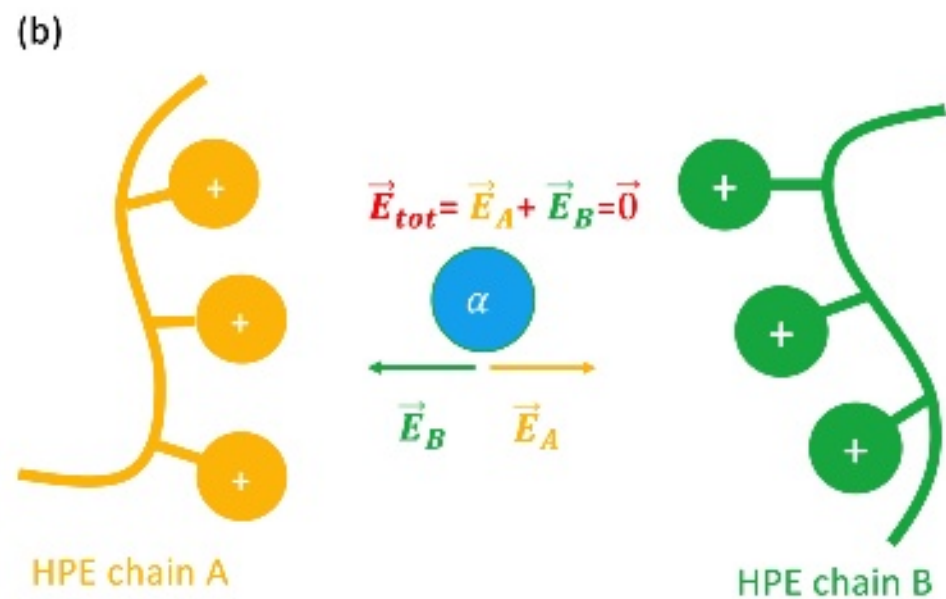
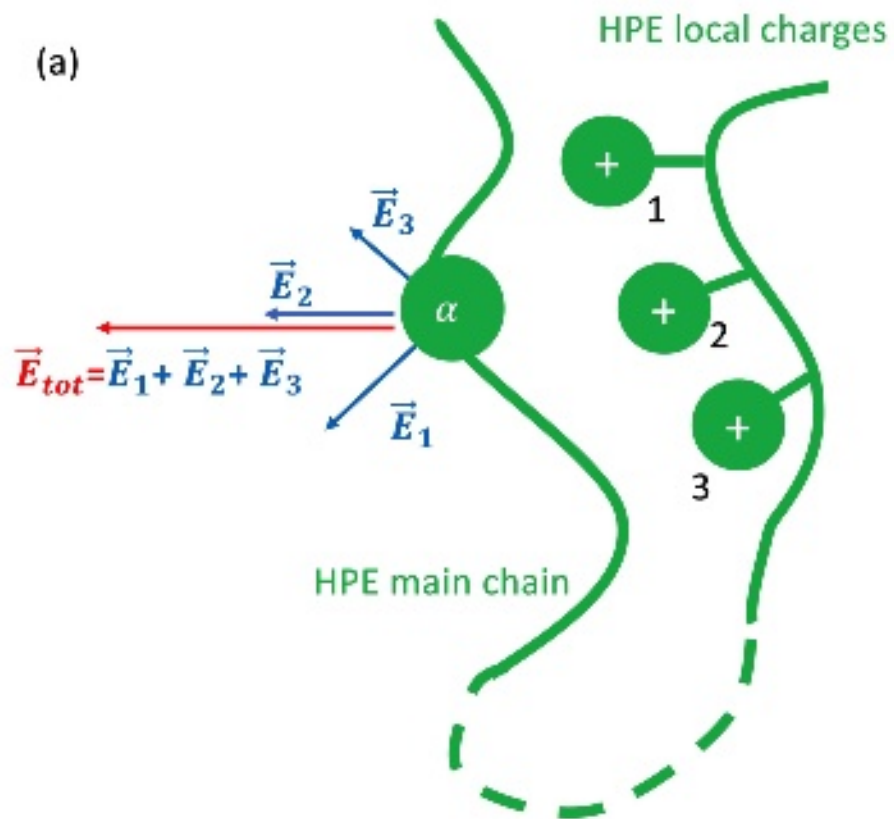
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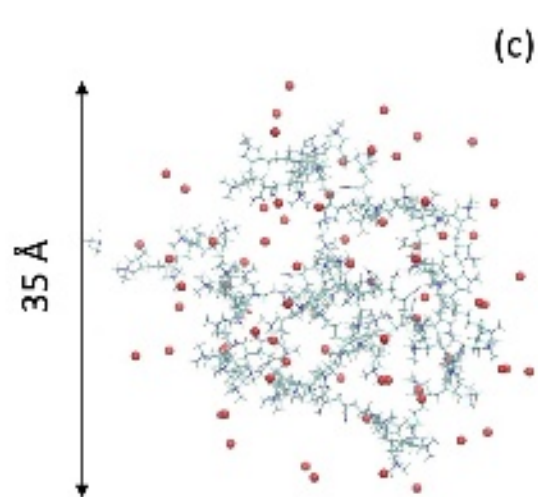
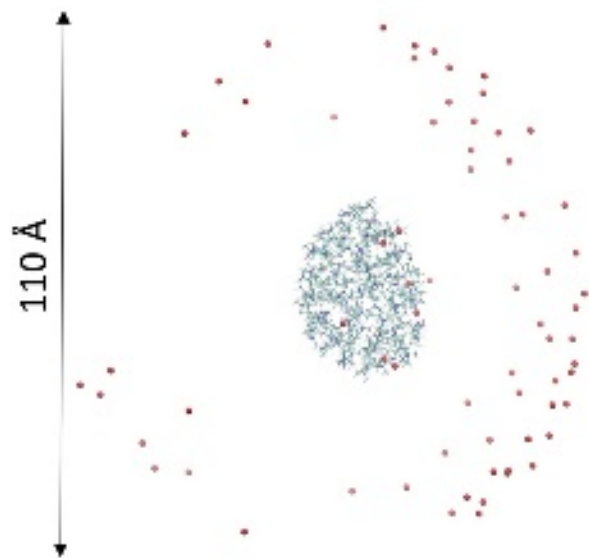
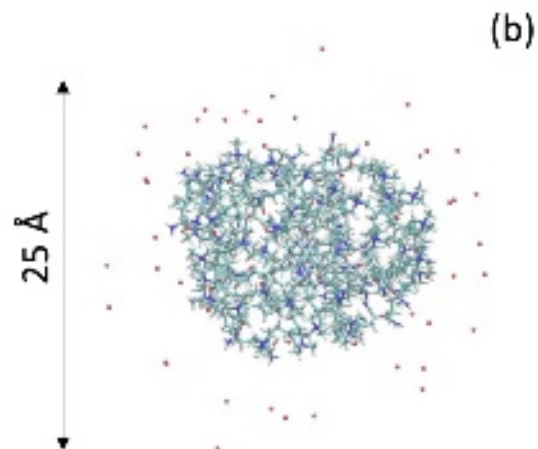
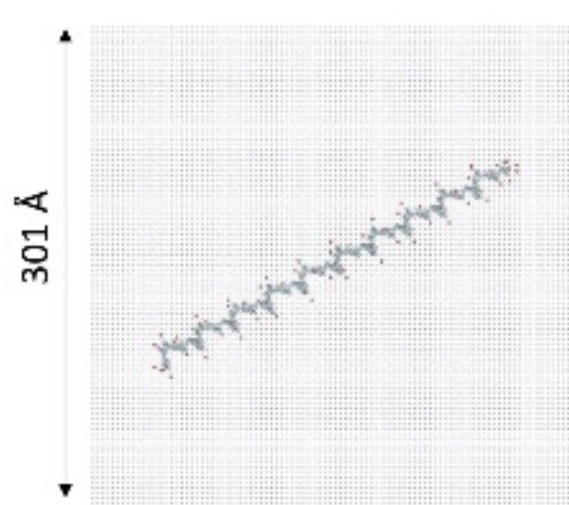
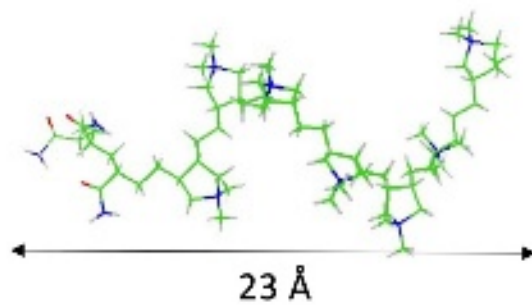
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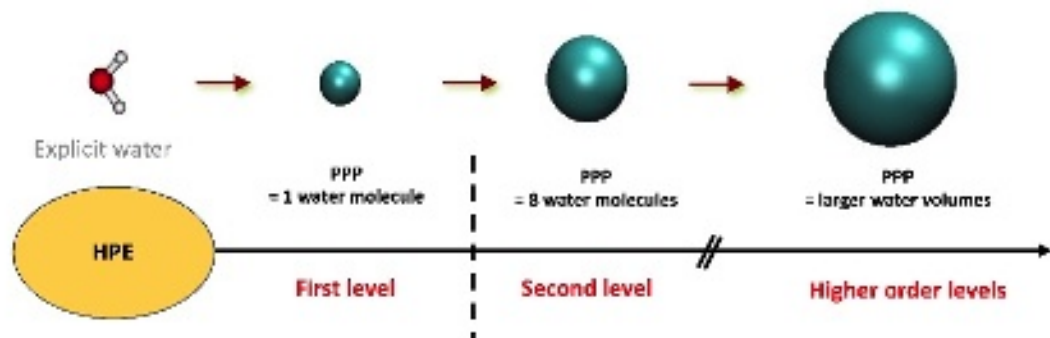
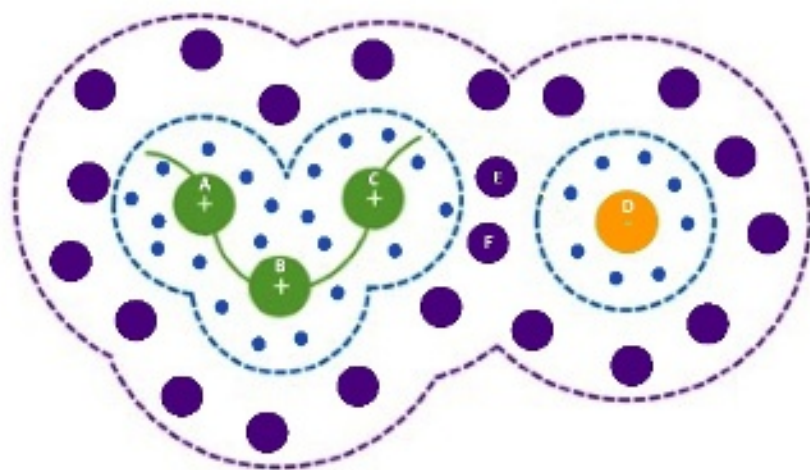
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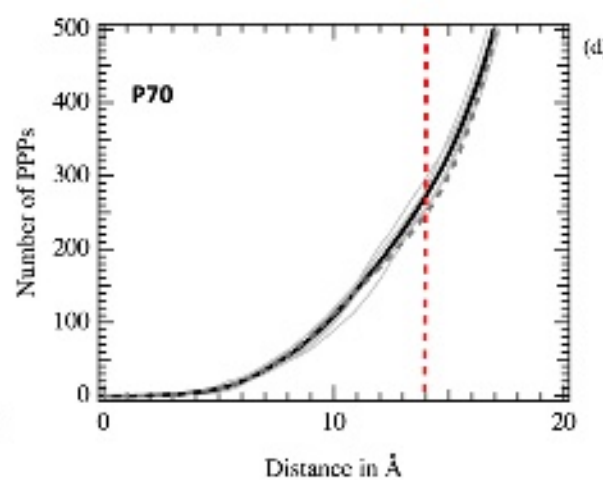
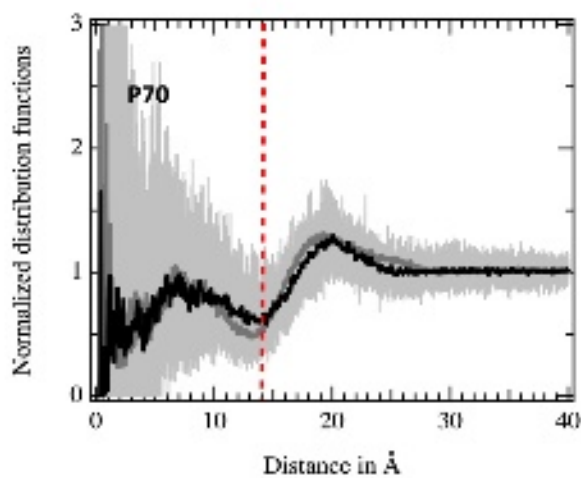
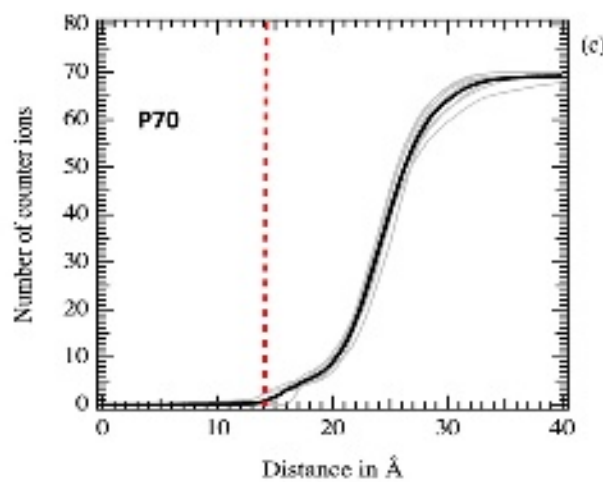
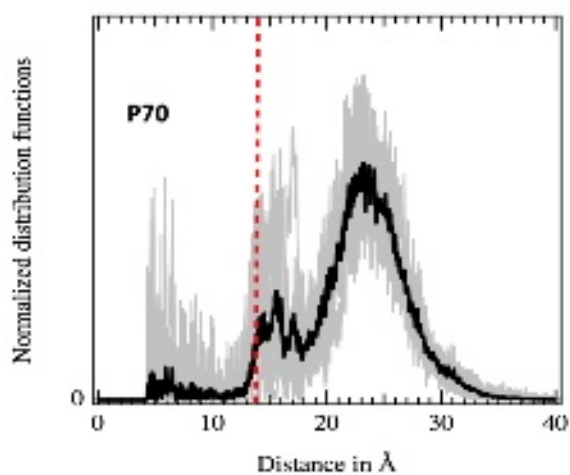
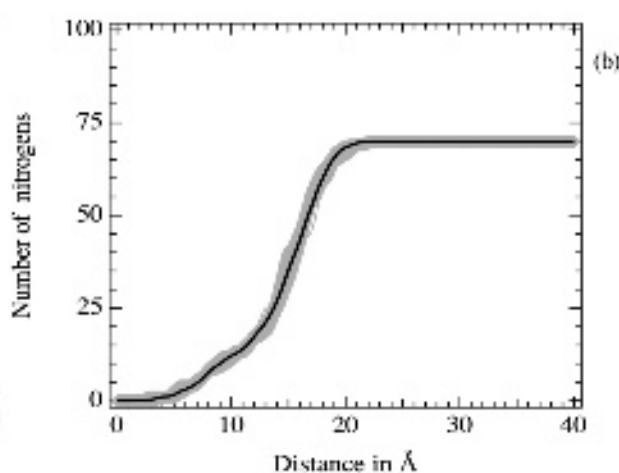
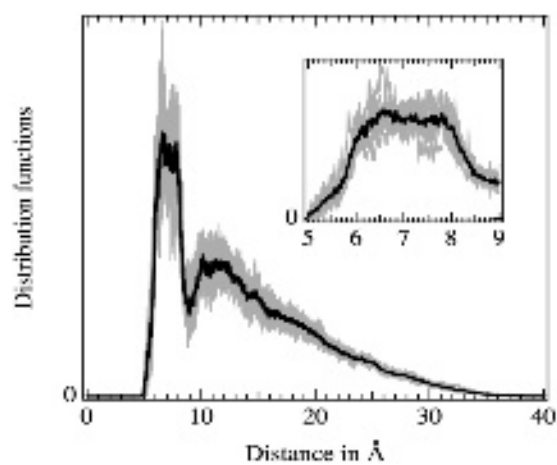
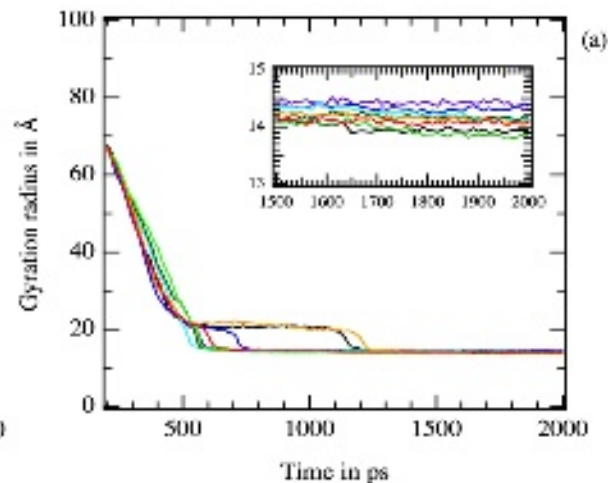
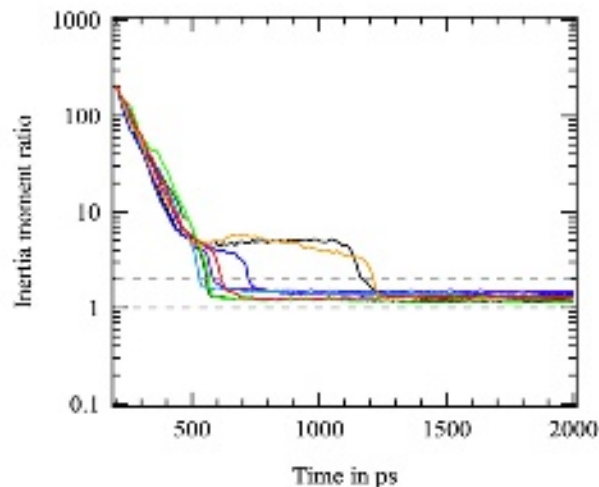
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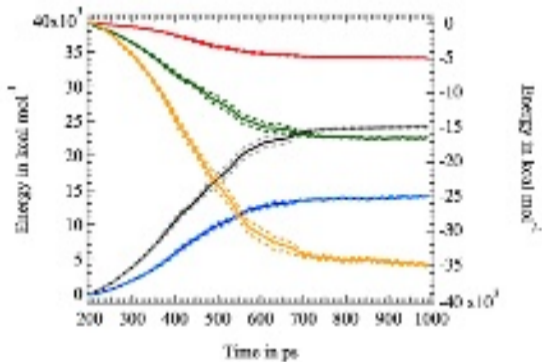
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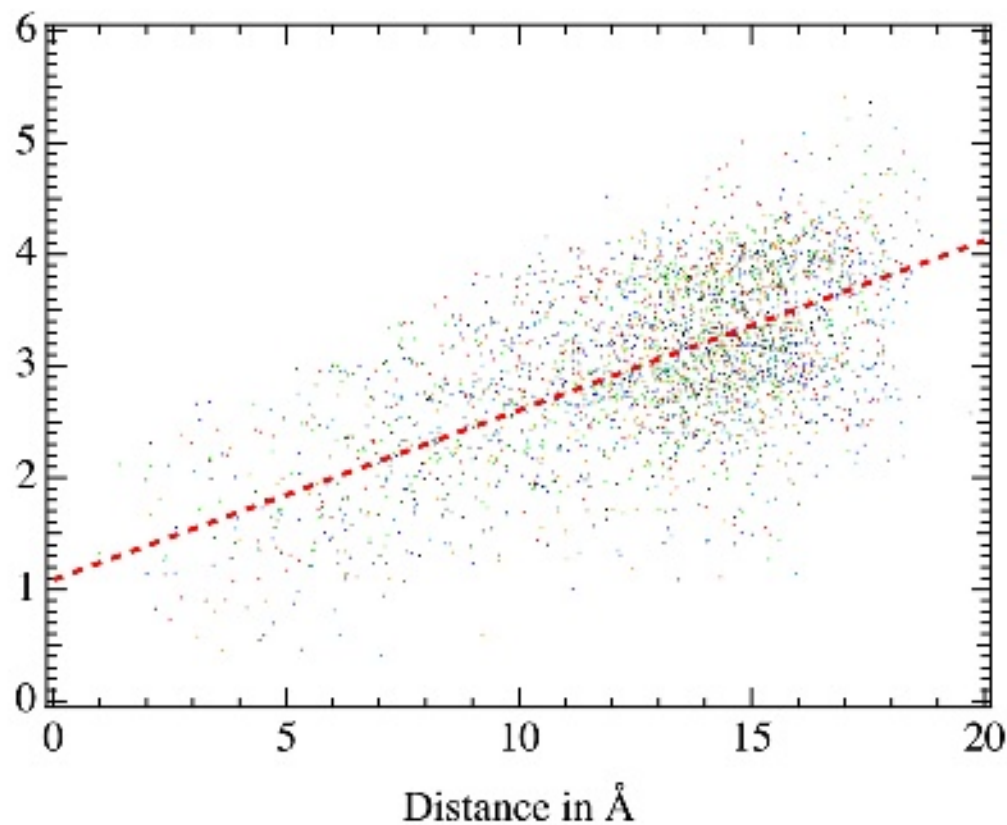


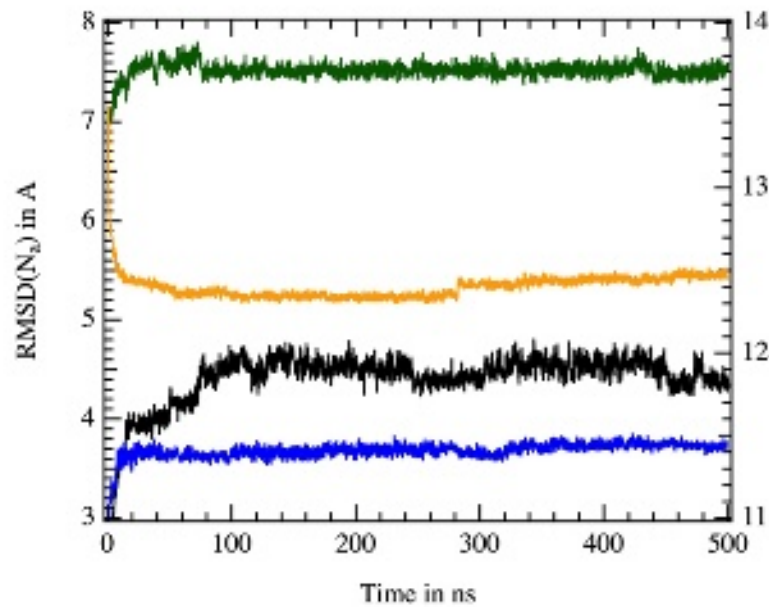
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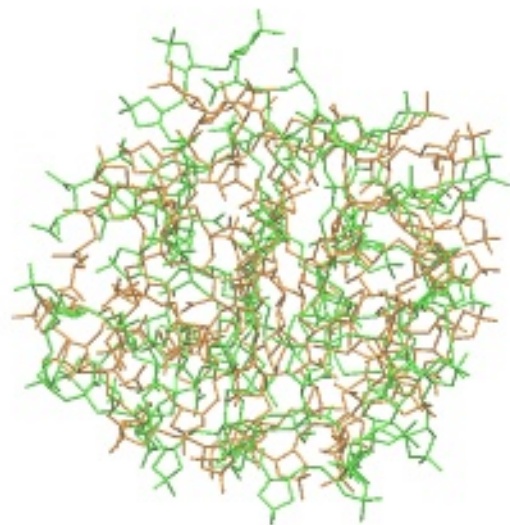


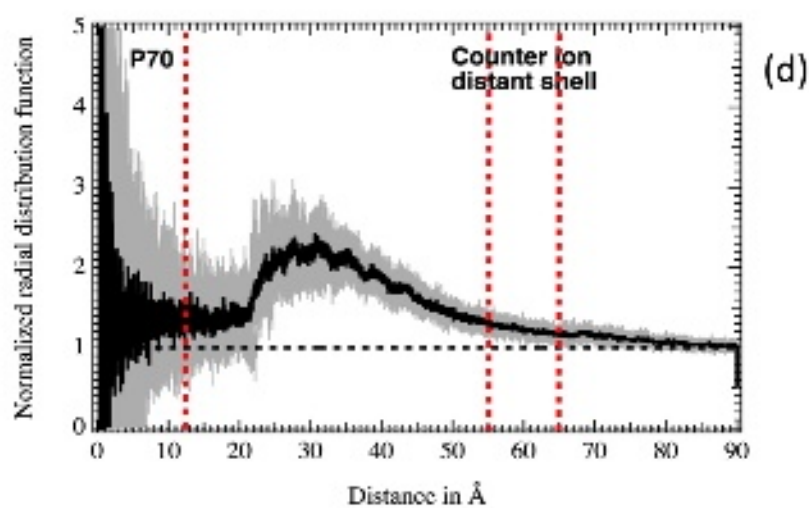
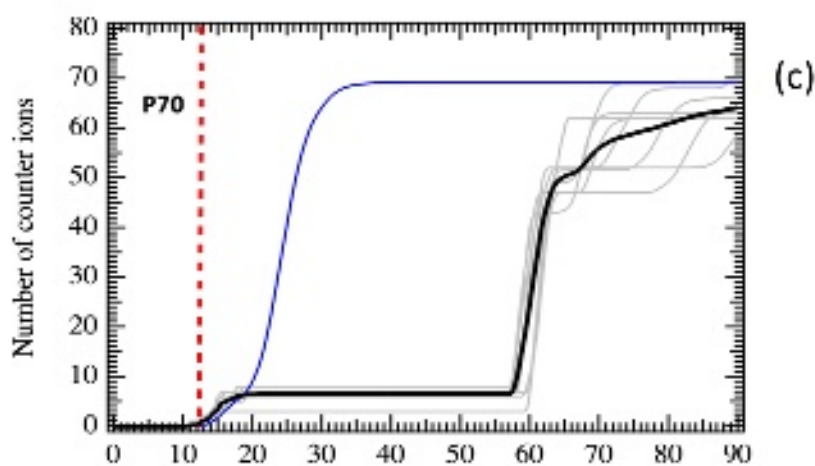
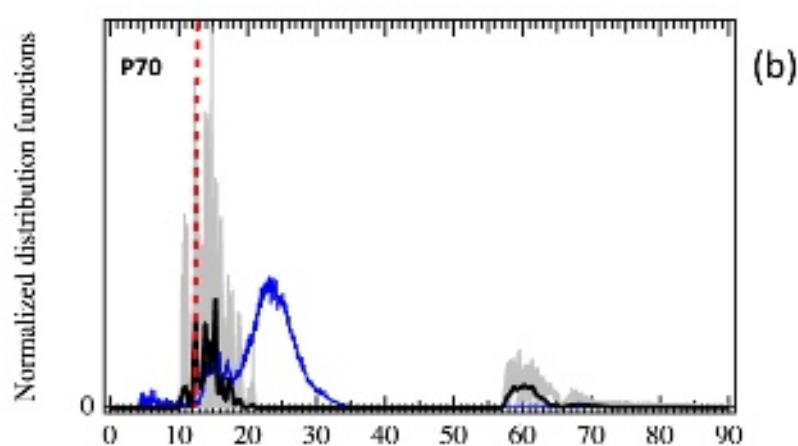
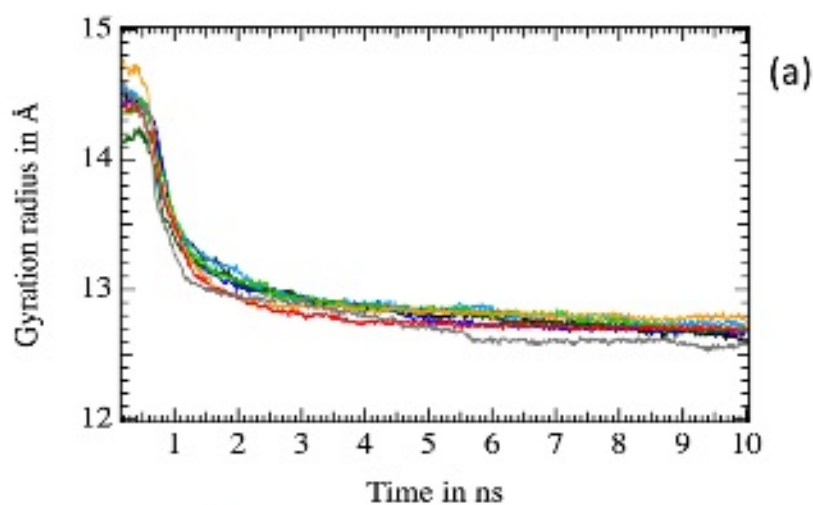
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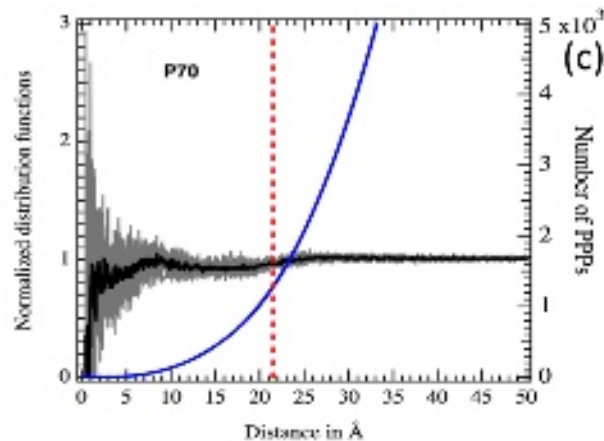
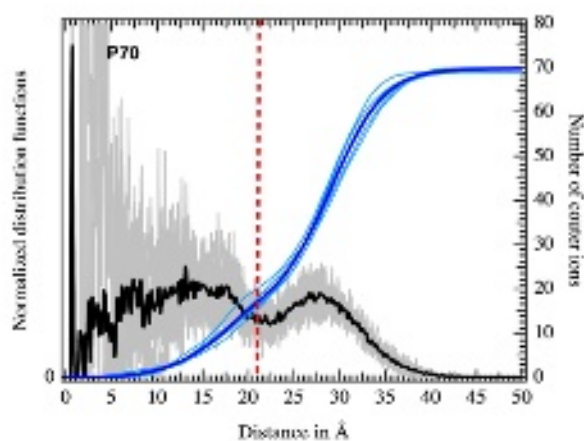
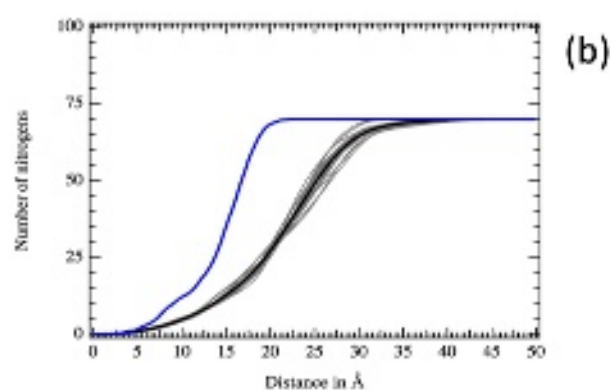
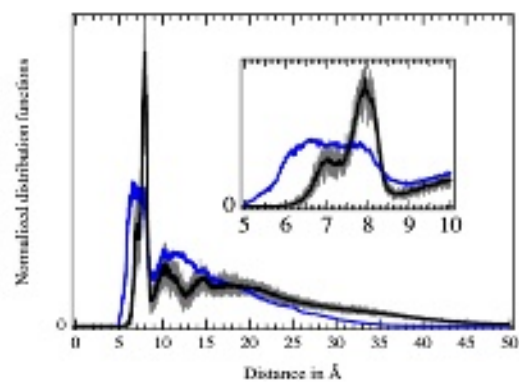
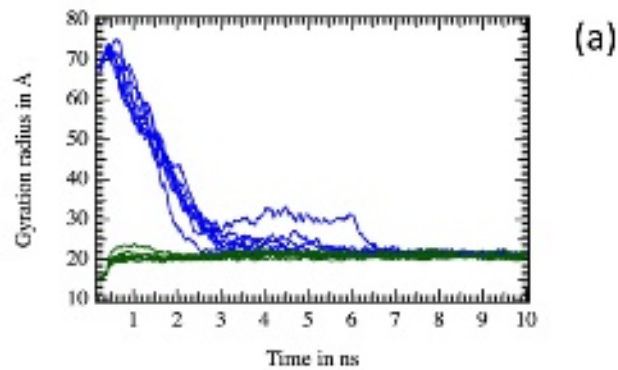
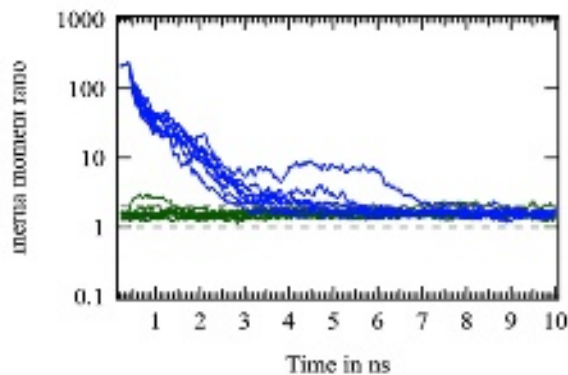


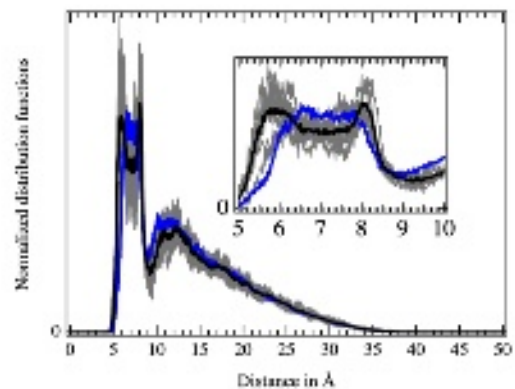
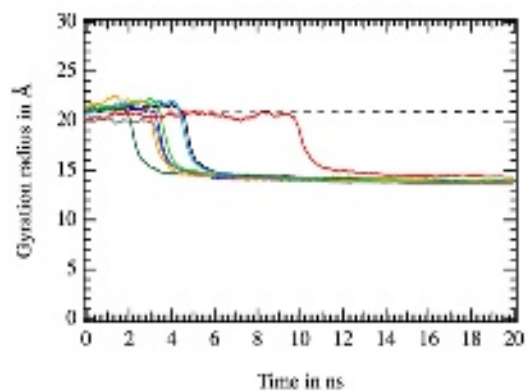


Gyration radius in Å

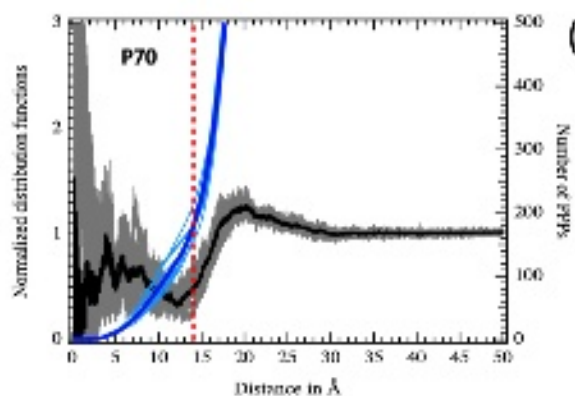
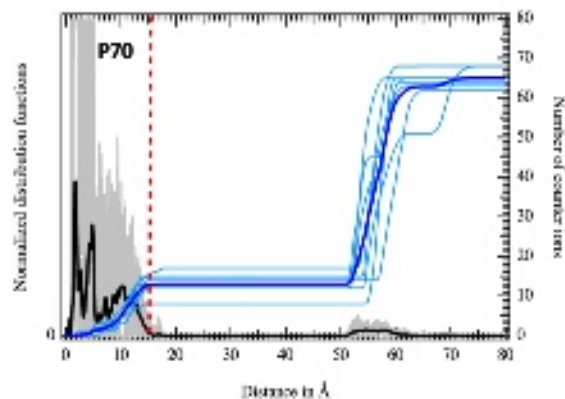








(a)



(b)

